A STUDY OF ASSOCIATION OF LOW SERUM TESTOSTERONE AND PROSTATE CANCER BEHAVIOUR

Dissertation submitted to

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In partial fulfillment of requirements

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M.CH (UROLOGY) –BRANCH -IV

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DECLARATION

I solemnly declare that this dissertation entitled, **"A STUDY OF ASSOCIATION OF LOW SERUM TESTOSTERONE AND PROSTATE CANCER BEHAVIOUR"** is a bonafide work done by me in Department of Urology, Rajiv Gandhi Government General Hospital, under the guidance and supervision of the Professor **R.Jeyaraman,M.S,M.Ch(Uro).,**Professor and Head of Department, Department of Urology, Madras Medical College & Rajiv Gandhi Government General Hospital ,Chennai. This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, in partial fulfillment of requirement for the award of Degree of **M.Ch Urology.**

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INDEX

INTRODUCTION

Prostate cancer is one amongst the most common medical diseases affecting elderly men. Carcinoma of the prostate is being the most common non-cutaneous cancer diagnosed in American male population. The lifetime risk of prostatic carcinoma is 16.7 % and the risk of death during the entire lifetime is around 2.6% for men in United States but the overall lifetime risk of death due to prostate malignancy is low in comparison to lifetime risk of diagnosis.

In developed countries carcinoma of the prostate gland is more common in the elderly male population compared with younger men. Around 15% of men diagnosed to have cancer of the prostate in developed world when compared to only about 4% of men in developing nations.

The association of cancer prostate and serum testosterone is known for the past few decades. The benefits of surgical castration and the role of estrogen treatment on the management of metastatic cancer prostate was assessed since olden days (Huggins and Hodges, 1941).They earlier demonstrated the clinical beneficial effects of androgen suppression therapy in the management of metastatic (advanced) cancer prostate.

The androgen suppression benefits are recently extended in the management of even in non metastatic prostate cancer patients and recurrent prostate cancer after definitive management. Again there is a role for hormonal therapy in

neoadjuvant settings like before radical prostatectomy which resulted in decrease in serum PSA, Shrinkage of prostate tumor volume and reduction in the rate of positive surgical margins. The reduction in prostate volume following neoadjuvant hormonal therapy is more in peripheral zone compared to central zone.

Prostate cancer is a hormone dependant cancer and the clinical course of prostate cancer varies with individual and again it varies within the individual in relationship to serum testosterone levels. The present study is to find out the role of low serum testosterone level in predicting prostate cancer behaviour in comparison with normal serum testosterone level patients and to find out the relationship between low serum testosterone level and serum PSA levels in TRUS biopsy proven cancer prostate patients.

AIM AND OBJECTIVES

The primary aim and objective of our study is to determine the association of low serum testosterone and prostate cancer behaviour and with a Secondary objective to determine the relationship of serum PSA level in cancer prostate patients with low serum testosterone.

REVIEW OF LITERATURE

Anatomy of the prostate gland:

Zonal Anatomy:

The prostate gland is analogous to the shape of an inverted pear with broader base of the prostate located cranially and the narrow prostatic apex caudally. The prostatic gland is composed of 15 to 30 branched tubuloalveolar glands which in turn embedded in a stroma of connective tissue and smooth muscles.

The prostatic glands are outgrowths of the mucous membrane of the urethra, ends in excretory ducts which in turn open into the prostatic urethra at and below the level of verumontanum. The paired ejaculatory ducts also open into the prostatic urethra at verumontanum level. The ejaculatory duct is formed by the union of the ampulla of the ductus deferens and Seminal vesicle duct just before terminates into the posterior aspect of the base of the prostate.

The prostate gland is distinguished into three glandular regions namely a central zone, a transition (periurethral) zone, and a peripheral zone[2].

In young male population the peripheral zone occupies 70-75% of the total prostatic volume and the central zone occupies 25% and nearly 5% of the gland by the transition zone.

The zonal composition changes with age. The central zone is more in young men and as the age advances it undergoes progressive atrophy and sometime reduction in size of the gland but in most men there is overall increase in prostatic glandular size due to benign prostatic hypertrophy involving transition zone. The peripheral zone is most important site of origin of prostate cancer.

The central zone is composed mainly of stoma and compact smooth muscle bundles but the peripheral zone smooth muscle bundles are loosely arranged with abundant glandular component. The peripheral zone is located along the lateral and posterior aspect of the prostatic gland surroundings the central zone.

The central zone is embedded between the anteriorly placed transition zones and postero-laterally placed peripheral zone.

At the level of verumontanum, the urethra makes an age of 35°. The distal prostatic portion of urethra is in close contact with the periurethral glands and preprostatic sphincter.

The preprostatic sphincter is formed by the striated muscles and surrounds the proximal portion of the prostatic urethra between the base of the verumontanum and the bladder neck area. The zonal anatomy of prostate gland is as shown in figure 1.

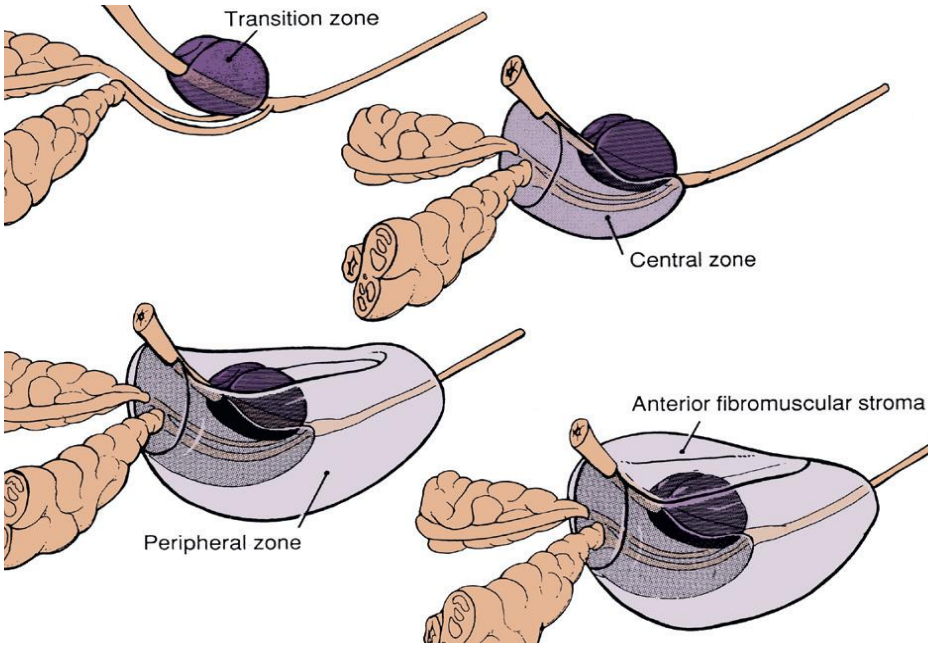

Figure 1.zonal anatomy of prostate gland.

The distal prostatic urethra is surrounded by striated muscle bundle which merge distally beyond the apex of the prostate gland with external sphincter.

The anterior fibromuscular stroma mainly composed of smooth muscles blends with the muscle fibers at bladder neck and surrounds the urethra, the anterior muscle fibers extends from the bladder neck and spreads laterally and covers the entire anterior and antero lateral aspect of the prostate gland.

The prostate gland is enclosed by capsule about 1 mm in diameter which consists of fibromuscular strands and extends into the pubovesical ligments and muscles. The fibromuscular strands which surround the prostate are an intrinsic and inseparable part of the prostate gland which is incompletely formed at the apex.

NEURO VASCULAR ANATOMY:

The arterial supply of the prostate gland originates from inferior Vesical artery and middle hemorrhoidal branches of the internal iliac artery.

The veins from prostatic plexus which covers the gland more on the lateral aspect. The prostatic venous plexus communicates with hemorrhoidal plexus posteriorly and with vesical venous plexus and venous plexus of Santorini's superiorly and drain into the internal iliac veins. The nerve supply are derived from pelvic plexus and is distributed mainly to connective tissue around the gland. The Neurovascular bundles NVBs are most important periprostatic structures which consist of sympathetic nerves, arteries and veins of the prostate gland. The paired NVBs runs along the postero lateral aspect of the prostate and gives periodical branches which pierces the prostatic capsule to reach the prostate gland.

The surgical anatomy of the prostate gland is depicted in the figure 2.

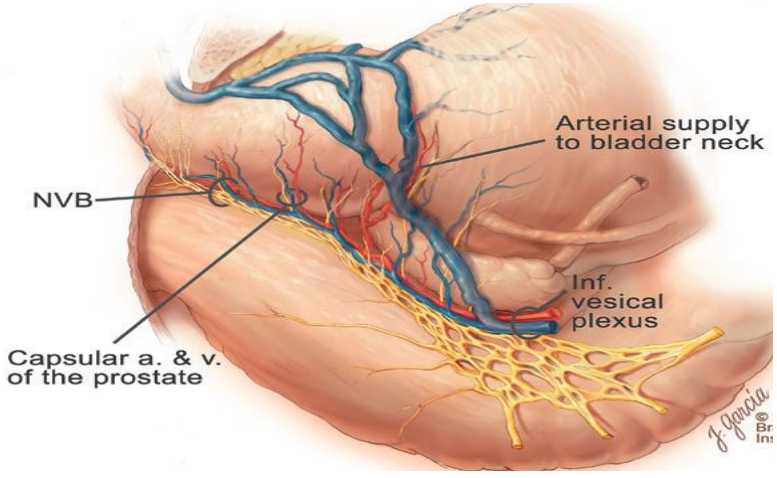

Figure 2. Surgical anatomy of prostate gland.

The extra capsular spread of prostate cancer occurs along the sites of penetrating branches of NVBs into the prostate capsule. While performing “Nerve Sparing” radical prostatectomy, the surgeon aims to preserve potency by sparing one or both NVBs.

LYMPHATIC DRAINAGE:

The Lymphatic drainage of the prostate gland is rich and forms a network over the posterior aspect of the prostate. The lymphatic from this posterior surface drains into the internal iliac group of nodes and the “obturator nodes” of the external lymphatic chain.

PROSTATE CARCINOMA:

EPIDEMIOLOGY:

Cancer of the prostate gland is a major public health problem in men aged 40 years and above and is comparable with that of women with breast Cancer. The Prostate Carcinoma is the most common cancer in American men (excluding skin carcinoma) and is the second in the list of common cancers in men.

The median age at the time of cancer prostate diagnosis is around 68 and more than 60% of carcinoma prostate is made above the age of 65. There is a significant variation in the geographic distribution of prostate cancer incidence.

The serum Prostatic Specific Antigen (PSA) testing has revolutionized the prostate cancer detection rate and is an important marker for diagnosis of cancer prostate. Serum PSA testing results in the increase in the number of patients localized prostate carcinoma and reduction in the advanced (metastatic) disease of cancer prostate. Serum PSA testing has resulted in downward stage migration of disease as well as early age at the time of diagnosis.

Genetics and environmental factors contribute significantly in the development of the cancer prostate. Chronic inflammation may possibly play role in the development of cancer of the prostate gland.

Androgens and possibly estrogens contribute significantly in the pathogenesis of prostate cancer development.

Prostate cancer risk is added to some extent by the presence of excess growth factors and possibly by dietary factors like saturated fat.

HISTOLOGICAL VS CLINICAL CANCER:

Controversies in the prostate cancer management occur in relation to several unique features of prostate. First, most prostate malignancy do not lead to serious morbidity or mortality.

Autopsy studies and prevalence rate of prostate carcinoma in cysto prostatectomy specimens have shown about 30-46% of men aged 50 years and above have microscopic prostate cancer, but still less than 20% of men will develop clinical prostate malignancy in their lifetime.

Second, the natural history of prostate malignancy covers a wider spectrum of biologic activity unlike the natural history of most other malignancies (e.g. Lung, colon, breast or ovarian cancer) which behave aggressively and are uniformly fatal if left untreated.

Some prostate cancers are small, well differentiated and unlikely to cause clinical disease while others are larger, poorly differentiated and more likely to undergo metastases and progress to death.

There are several hurdles in the optimal management of prostate cancer. An important challenge is related to screening, is to differentiate latent subclinical cancer from clinical prostatic carcinoma.

Majority of prostate cancers detected through an early detection program represent clinical rather than latent cancer and these group of patients are detected at an early stage of the disease. Prostate cancer screening in general population is controversial and based on the conclusions from two large randomized controlled trials, majority of the urological bodies report that currently mass screening for cancer prostate is not necessary.

Cancer prostate detection at an early period should be suggested for men who are willing to undertake the test after informed consent. The baseline prostatic specific antigen (PSA) estimation can be done at the age of 40 years and subsequent screening interval as per the baseline value. If the initial PSA value is ≤ 1 ngm/ml patient may be screened of an interval of 8 years. For men older than 75 years the test may not be that much essential as per some authors report.

CLINICAL AND PATHOLOGICAL PRESENTATION:

Prostate cancer may present asymptomatic while detected by screening or early opportunistic detection program. Patient may present with symptoms and signs prostatism like hesitancy, poor-urinary stream, and increase frequency of micturition and rarely present with Hamaturia. prostate cancer patient may present with bladder outlet obstruction though Benign prostatic Hyperplasic (BPH) is most frequent etiology.

Patient may present with Bladder diverticula, uremia due to distal ureteric obstruction, bone pain or pathological fractures due to bone metastasis. Patient may present with local hemorrhage due to necrosis of tumor or generalized bleeding due to liberation of large quantities of prostatic fibrinolysin, patient may present with hydroureteronephrosis either unilateral or bilateral. Urinary tract obstruction suggests an ominous prognosis.

Majority of prostate cancer begins in the peripheral zone and an adeno carcinoma being the most common (>95%) histology with variable degrees of differentiation. Cancer prostate may also arise from transition zone followed by central zone.

Transitional cell carcinoma, squamous cell carcinoma and rarely prostatic sarcoma may be found. Most prostatic adenocarcinoma develops from tubulo alveolar glands but the rare ductal prostatic cancers also can occur and have a poor prognosis. Poorly differentiated prostate cancers have more chance of having a pelvic lymph nodal involvement and poorer prognosis.

DIAGNOSIS:

Prostate Carcinoma is suspected because of an abnormality in digital rectal examination (DRE) or increase in serum PSA level.

DIGITAL RECTAL EXAMINATION:

Most of cancer prostate are identified in the peripheral areas of the gland may be made out by digital rectal examination when tumour burden is about 0.2ml or more. Cancer prostate is detected by DRE abnormality alone in 18% of patient irrespective of PSA values. DRE abnormality in patient with a prostate specific antigen value of up to 2ngm/ml has positive prediction value for cancer in five to thirty percentages. Digital rectal examination variations is an important indication for taking prostatic biopsy as it is a predictor of more vigorous cancer prostate. Studies have shown that the PSA increase due to DRE is not clinically significant.

Prostate specific Antigen (PSA):

The diagnosis of cancer prostate has been revolutionized by the measurement of serum PSA level. PSA is produced almost exclusively by the prostatic epithelial cells and belongs to Kallikrein family. Serum PSA levels may be increased in conditions like prostatitis, Benign prostatic hyperplasic (BPH), and also in other nonmalignant conditions apart from prostate cancer. The PSA level is an independent variable and better predictor of prostate carcinoma than abnormal findings in DRE or by Transrectal Ultra Sound (TRUS) examination.

Several modifications of serum PSA level have been identified and described to improve the PSA specificity in the early and better detection of cancer prostate. These include PSA density, transition zone PSA density, Age-specific PSA reference range, and other PSA molecular forms.

In routine clinical evaluation these PSA derivatives and isoforms of PSA have very limited usefulness.

Free/Total PSA ratio:

The ratio of free PSA to total prostate specific antigen is the current concept evaluated and used in clinically to differentiate benign from cancer prostate. The ratio is useful for men with prostate specific antigen levels between four and ten ngm/ml and a normal digital rectal examination. Prostate cancer risk is more than 50% if the free total PSA ratio is <0.10 and prostate cancer risk falls to <10% if the ratio is >0.25. In addition the free to total PSA ratio is not useful if total PSA is >10ngm/ml and during follow-up cancer prostate patients.

PSA Velocity (PSA-V):

PSA velocity is expressed in ngm/ml/year and is calculated as the increase in PSA per year. The increase in PSA of more than 0.75ngm/ml/year has got more risk of prostate cancer.

PSA Doubling Time: (PSADT)

It is defined as the time duration required for the patients PSA value to double in months or years. PSADT is useful in cancer prostate patients under surveillance for elevated PSA but negative prostatic biopsies, for active surveillance and for follow-up of rising PSA level post radical treatment.

PSA Density: (PSAD)

PSA density is calculated as the serum PSA value per ml of prostatic tissue. Prostate volume can be measured by the following formula

Prostate volume = Length X height X width X 0.52

A PSAD value of >0.15 ngm/ml of prostate gland has got more chance to lead to cancer prostate.

TRANSRECTAL ULTRASONOGRAPHY (TRUS):

TRUS is very useful and mandatory for taking prostate needle biopsies. TRUS showing hypoechoic lesion in the peripheral zone of the prostate has better yield of cancer than isoechoic or hyperechoic areas.TRUS with help of colour Dopler study will be useful for better visualization of prostate cancer as shown in figure.3.

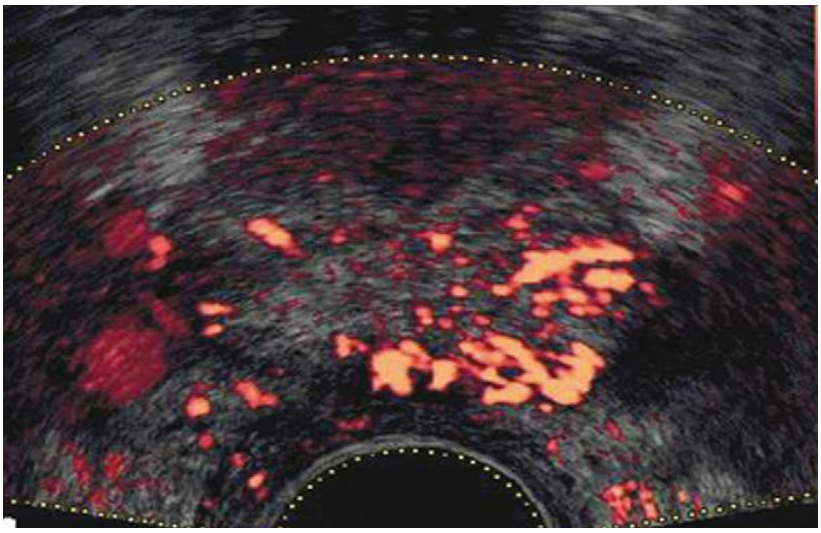

FIGURE 3. TRUS WITH COLOUR DOPPLER STUDY

PATHOLOGY OF PROSTATE CANCER:

The Gleason grading in the more commonly used and widely accepted for prostate cancer. Gleason score is an independent prognostic factor for assessing the clinical behavior and treatment. It is based on the glandular architecture of the prostate tumour identified under low power magnification. A cytologic characteristic has got no role in the grading system. The architectural patterns includes the primary or predominant pattern and secondary or second more common pattern are identified and assigned a grade from one to five, with 5 being least differentiates and 1 being well differentiated.

The various Gleason grades have been depicted in the following figure 4 to 8.

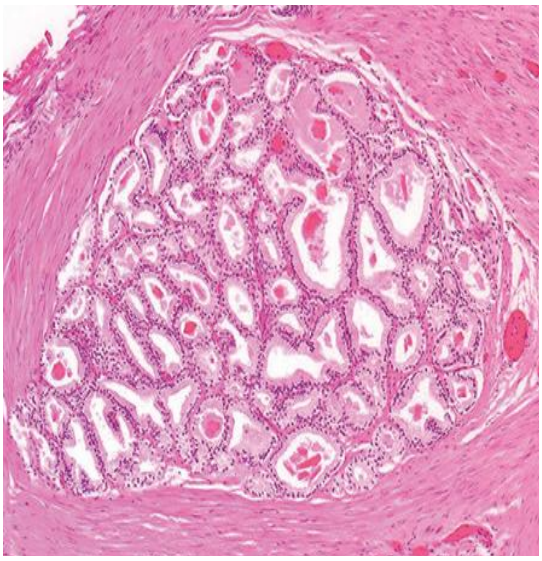

Figure 4.Gleason grade 1

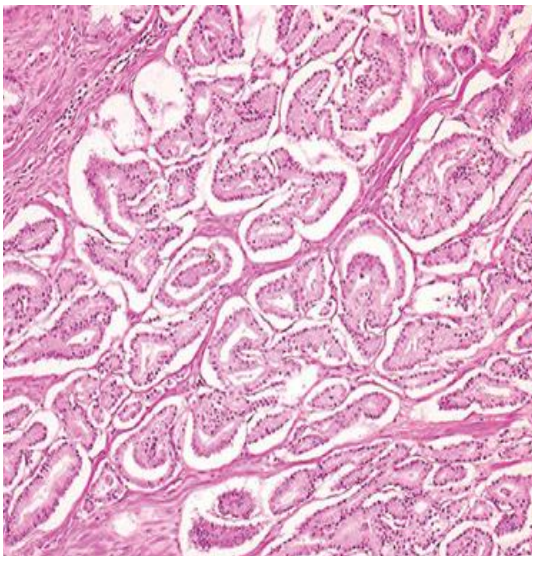

Figure 5. Gleason grade 2

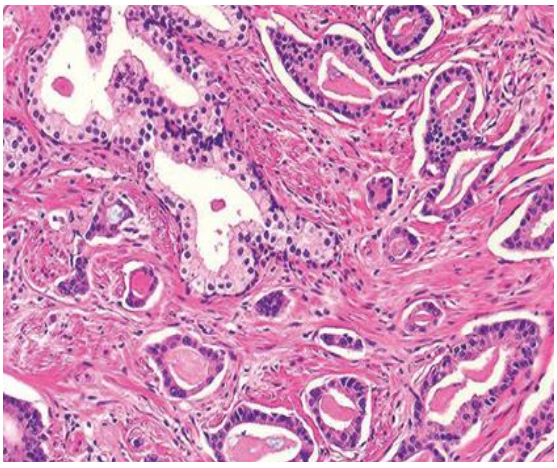

Figure 6.Gleason grade 3

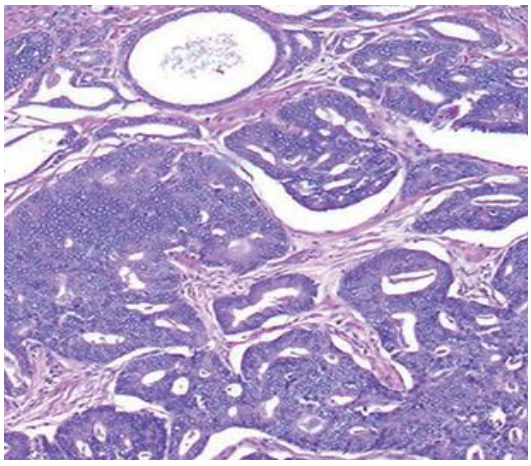

Figure 7.Gleason grade 4

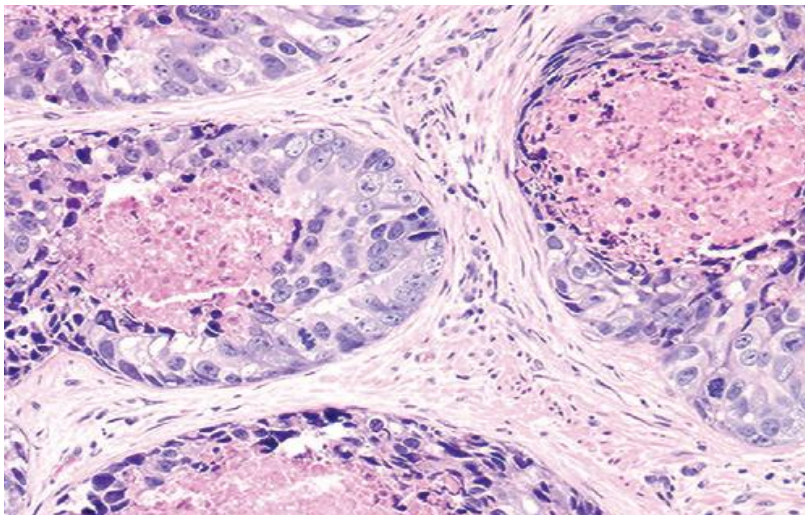

Figure 8. Gleason grade 5

The prognosis of prostate cancer is based on the score obtained from sum of primary and secondary Gleason grades.

A tertiary Gleason grade of 4 or 5, if in excess of 5% of total prostate cancer volume indicates an unfavorable prognosis and predictor of biochemical recurrence.

Gleason scores range between 2 and 10.

Studies have shown that the Gleason score can be improved by eliminating Gleason scores 4 or Lower for adenocarcinoma of prostate on TRUS guided needle biopsies.

The length in mm and percentage of cancer involvement per biopsy is best correlated with extra prostatic extension, tumour volume and prognosis following radical prostatectomy. Percentage of cancer involvement in biopsy and length of cancer involvement in mm are of equal prognostic value.

HISTOPATHOLOGY OF RADICAL PROSTATECTOMY SPECIMENS:

The objectives of histopathological examination of radical prostatectomy specimen are to obtain information about pathological stage, exact Gleason grade, and surgical margin status, location, extent of extra capsular extension or seminal vesical invasion & bladder neck involvement of the cancer prostate. Processing of prostatectomy specimen by total embedding technique is preferred. The presence of prostate cancer beyond confines of the prostate extra prostatic extension is in indicated by extra prostatic extension includes tumour involvement of periprostatic adipose tissue invasion of neuro vascular bundle or the anterior prostate and invasion of the bladder neck.

Surgical margin positivity is an important and definite risk factor for postoperative recurrence. Margin status is taken as positive if tumour cells are in contact with inked surface and negative when tumour cells are away from inked surface or close to inked surface.

STAGING OF CANCER PROSTATE BY CLINICAL ASSESSMENT:

The initial workup of cancer prostate patient is done by digital rectal examination, serum prostate specific antigen measurement and extension of assessment made by bone scan with supplementation by CT scan or MRI and chest x-ray as required.

T STAGING:

Local tumour stage is done by T Staging where the difference between intracapsular (T_1-T_2) and extra prostatic involvement (T_3-T_4) has more important impact on treatment decisions and patient outcomes.

DRE often underestimates the prostate cancer involvement and positive predictive value of DRE and pathological tumour stage was <50%. Serum PSA values increases as the age advances and it has got limited potential to predict the ultimate pathological stage. Serum PSA, Gleason biopsy score and clinical T stage have been proved to be more useful in assessing the final pathological stage of the cancer prostate.

TRUS not accurately stage the disease and hence currently TRUS is not used for local tumour (T) staging and is done with either CECT or MRI of Abdomen and Pelvis may predict the local staging and also assess the neurovascular bundle involvement.

Nodal Staging:

Nodal staging should be done only when the nodal involvement alters the management option. Nodal staging is routinely done when curative or definitive treatment is planned. High risk of nodal metastasis is predicted by the following factors high serum PSA levels, Stage T_{2B} & T_3 tumour, poorly differentiated tumour and presence of perineural invasion current literature suggest that pelvic nodal metastasis is better staged with CT or MRI although CT Scan is marginally superior to MRI. Lymph nodal metastasis is considered when the Lymph nodal size of 0.8cm for round nodes and around one cm in short axis for oval lymph nodes and was rated in either CT or MRI. Patients with PSA <20ngm/ml, Gleason Score of ≤ 6 and ≤stage T_2 have got a <10% glance having nodal disease and can be spared from nodal evaluation.

Pelvic Lymph nodal dissection provides the optimal staging in patients with clinically localized cancer prostate.

Metastasis:

Majority of cancer prostate patients die from axial skeleton metastasis. The prognosis of patients with cancer prostate is predicted by the presence and extent of bone metastasis, measurement of alkaline phosphates (skeletal) and serum PSA at the same time better predicts clinical outcomes.

Most sensitive method of assessing bone metastasis is by bone scintigraphy and is superior to skeletal survey, clinical examination & measurement of serum alkaline phosphates.

The current radiopharmaceuticals available for better evaluation of bone metastasis is technetium diphosphonates because of better bone to soft tissue uptake.

Prostate cancer spread mainly to bone and is followed by lymph nodal areas, Lungs, Liver, central nervous system & Skin.

Serum PSA is currently maker of choice for predicting the metastasis in cancer prostate patients. Current indications for bone scan in asymptomatic cancer prostate patients include serum PSA>20ngm/ml, Gleason Score ≥8, clinical stage T_3 & T_4.

MANAGEMENT:

RADICAL PROSTATECTOMY:

At present, radical prostatectomy is the recommended treatment option for patient with localized cancer prostate with better overall survival time and cancer specific survival period compared with conservative treatment.

Radical prostatectomy involves excision of whole prostate tissue between the bladder and urethra, and removal of both seminal vesicles along with adequate tissue all around to obtain negative tumour at the margins, along with bilateral pelvic lymph nodal dissection. In cancer prostate patient with localized disease and a life expectancy of $\geq$ 10 years is to achieve disease eradication, preservation of urinary continence and erectile function.

Life expectancy is atmost importance in counseling for radical prostatectomy in a prostate cancer patients. No patients should be denied of curative radical prostatectomy merely based on chronological age .

Radical Prostatectomy is carried out by open approach either by retropubic method or by perineal and recently minimally invasive methods like robot assisted laparoscopic Prostatectomy (RALP) and Laparoscopic Radical Prostatectomy (LRP) are progressing rapidly.

Radical Prostatectomy is currently recommended for patients with T_{1c} tumours, T_{2a} and also in patient with intermediate risk group like T_{2B}-T_{2C}, Gleason score > with PSA 10-20ngm/ml group.

Radical Prostatectomy is controversial in high risk localized disease with CT3A or Gleason score 8-10 & Serum PSA >20ngm/ml and is reasonable option only in selected patients with low volume prostate cancer.

HORMONAL THERAPY:

Hormonal injection of cancer prostate was started for the management of metastatic disease seven decades ago (Huggins & Hodges) and since then it is used in the management of advanced prostate cancer. Currently androgen suppression treatment is extended in the management of non-metastatic prostate cancer, in younger patient and in recurrent cancer prostate after definitive management.

Androgens are basically responsible for the stimulation of prostate cellular development, function and proliferation. Testosterone is critical for the growth & alteration of prostate cancer cells. Testes are the major androgen sources followed by adrenal androgen which occurs for 5-10% of androgens.

Testosterone is under the control of hypothalamo pituitary gonadal axis. Anterior pituitary gland is stimulated by Luteinizing hormone releasing hormone and in turn results in the release of Luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH activates testicular leydig cells to release testosterone inside the prostate cells 5 & dihydroxy testosterone are produced from testosterone by the action of (DHT) 5alpha reductase enzyme. DHT is more potent (10 times) than serum testosterone.

Testosterone in circulation is aromatized peripherally and metabolized to estrogens, which along with androgen exert a negative bio feedback action over hypothalamus.

Prostate cells undergo programmed cell death (apoptosis) if they are deprived of androgen stimulation effects. Currently androgen suppression therapy is widely used in the management advanced prostate cancer.

Mechanisms of Lowering Serum Testosterone:

Castration Level:

Surgical castration is considered the mainstay of androgen deprivation therapy against which other treatment options are compared. The standard castrate range is <50ngm/ml and few studies says it may be <20ngm/ml.

B/L Orchiectomy (Surgical Castration):

B/L orchiectomy either subcapsular or total is a simple, standard treatment option with negligible complication rate. It is usually preformed under local anaesthesia and a faster way attain a castration level within 12-24 hours. The disadvantage of surgical castration is it is irreversible and it exerts negative psychological effect on manhood.

Oestrogens:

Oestrogens exerts is hormonal effects by several mechanism like androgen inactivation, decrease in the LHRH secretion, control of Leydig cell function by direct action and cytotoxic action to the prostate epithelium (directly).

Diethyl stilboesterol (DES):

The commonly used oestrogen in cancer prostate the hormonal effects of DES are comparable to that of surgical castration. The cardiovascular adverse effect makes this drug less practiced than surgical castration.

LHRH agonist:

Currently LHRH agonist have been used widely in the management of advanced cancer prostate as an alternate to surgical castration. LHRH analogues are generally administered as depot injections on a monthly basis, or once in two to three months and occasionally twice a year basis. After an in initial injection they produce testosterone surge or LH "flare up" event which usually starts within 2-3 days and persists for about 7-10 days. The main disadvantage of LHRH agonist induced flare phenomenon results in worsening of bone pain, bladder outlet obstruction, spinal cord compression effect, and fatal cardiovascular effects because of hyper coagulation state. Simultaneous treatment with an anti androgen medication reduces the occurrence of clinical flare up response but still will not

totally suppress the flare risk. Anti androgen treatment should be initiated on the same day and continued for a minimum of 2 week period.

LHRH antagonists:

LHRH receptors are completely blocked by LHRH antagonist with an immediate effect which results in sudden fall in LH, FSH and serum testosterone values without LH flare events. This mechanism of action is more useful in avoiding flare response in advanced disease. The major drawback of LHRH antagonist is life threatening anaphylaxis due to histamine release. New generation LHRH antagonist may be occasionally useful to control flare-up with LHRH monotherapy in few symptomatic metastatic patients.

ANTIANDROGENS:

Two major classes of antiandrogens are namely steroidal and non-steroidal groups.

Cyproterone acetate:

First antiandrogen used and most commonly used drug in the past with half life of around 30-40 hours and administered orally 100mg each in twice or thrice daily dosing schedule.

NON STEROIDAL ANTI-ANDROGENS:

Non-steroidal antiandrogen when used as monotherapy compared with surgical castration has improved quality of life and better compliance. This group of drugs does not block the secretion of testosterone and maintains libido, Bone mineral density and Physical performance status. The common side effects includes liver toxicity, hot flashes, gynaecomastia and breast pain. Bicalutamide have shown better safety and tolerance than other drugs in this group.

COMBINED ANDROGEN BLOCKAGE:

Although surgical castration results in >95% reduction in serum testosterone levels, adrenal androgen secretion results in production of DHT in the prostate cells and results in continued androgen serum for the prostate cells. The adrenal sources of androgens can be completely controlled by adding an anti-androgen to either medical or surgical androgen suppression resulting in complete (total or maximal) androgen blockage (CAB) CAB offers small survival advantage <5% at the expense of increased cost and more side effects.

LOW SERUM TESTOSTERONE AND PROSTATE CANCER:

As the age advances serum testosterone level and cancer prostate incidence is on the higher side. Various studies have conducted and reported contrasting results with regards to serum testosterone level and cancer prostate risk.

Patients with low serum testosterone may present with clinical symptoms of loss of libido, depression and diminished bone mineral density and such condition is defined as hypogonadism.

Various studies related to cancer prostate and serum testosterone were analyzed by the endocrine and prostate cancer collaborative group and reported that there was no well defined association between cancer prostate and serum levels of testosterone, androstenediane, dihydrotestosterone (DHT) and estradiol levels. Older men with increased risk of cancer prostate had an association with low serum testosterone.

Few investigations have reported prostate cancer patients with low serum testosterone had worse prognosis and higher Gleason grade to metastatic cancer prostate compared with normal serum testosterone. Hence the purpose our present study is to find out the actual association between cancer prostate patients and low normal serum testosterone patients.Further studies are warranted to confirm the relationship.

MATERIALS AND METHODS

TITLE OF THE STUDY

A study of association of low serum testosterone and prostate cancer behaviour

PERIOD OF STUDY

March 2013 – February 2014

STUDY DESIGN

This study is a prospective study of analyzing the association of low serum testosterone and prostate cancer behaviour with patients with normal testosterone.

PLACE OF STUDY

The study was conducted in the Department of Urology, Madras Medical College and Rajiv Gandhi Government Hospital, Chennai- 3

ETHICAL CLEARANCE

The institutional ethical review board at our hospital approved the study.

Inclusion criteria

All newly diagnosed prostate cancer (TRUS guided biopsy proven) patients with age more than 40 years in our institution were enrolled .

Exclusion Criteria:

- Patients already on testosterone replacement therapy
- Patients on other hormonal therapy
- Men taking medications known to lower serum PSA level (Finasteride or Dutasteride)

Method of Study

Informed consent was obtained from all patients. All TRUS biopsy proven cancer prostate patients were enrolled to a maximum number of 100. All details were recorded as per the proforma (Appendix-3). Blood investigations like serum PSA, serum testosterone and other baseline investigations were obtained. The serum determinations of Testosterone obtained between 7 – 9.30 am. The serum Testosterone levels measured by appropriate standard protocols.

Patients were divided into two groups based on the serum testosterone levels. Patients with low serum testosterone levels (< 250 ng/dl) were categorized as Group A and patients with normal serum testosterone levels (> 250 ng/dl) were categorized as Group B and and the findings between two groups will be compared.

Clinical staging was done for all patients based on the findings in bone scan, Contrast enhanced CT Scan or MRI Scan of abdomen and pelvis. Surgery was done and all patients were followed up after one month of surgery.

All prostate cancer patients who were enrolled in this study were assessed at the time of admission based on detailed clinical examination, complete baseline blood investigations ,Serum PSA, Serum testosterone ,Gleason grading (TRUS biopsy) which includes primary ,secondary and total Gleason score or sum , Imaging studies (bone scan, CECT/MRI abdomen and pelvis and chest x-ray).

Patients with localized prostate cancers which include patients with Clinical stage T1 & T2 without regional pelvic nodal involvement and metastasis were counseled and given the option of radical prostatectomy (RP) and other patients who were in advanced stage of the disease which include clinical T3 and T4 disease and metastatic prostate cancer were managed with hormonal therapy in the form of surgical castration followed by anti-androgen therapy.

Patients who underwent radical prostatectomy (RP) were followed up post operatively with histopathological specimen analysis and parameters like post operative Gleason grade , pathological tumour (PT) status, pathological node (PN) status, surgical margin status (SMS), extra capsular extension (ECE) of tumour and seminal Vesical invasion (SVI) were compared between the prostate cancer patients with low serum testosterone (group A) and normal testosterone (group B).

Statistical analysis

The patient age and serum PSA were compared with the help of Student's t-test in the low- and normal serum testosterone groups. Chi-square test (Pearson's) was applied to compare the prostate cancer parameters between low and normal serum testosterone patients. Statistical analyses were done using software SPSS version 17.0. A p value equal to or below 0.05 was taken as statistically significant.

OBSERVATION AND RESULTS

Total of 106 patients with cancer prostate were taken into our study of which 5 patients on 5 alpha reductase inhibitors and 1 patient on testosterone replacement therapy were excluded from our study and finally 100 patients were enrolled in our study of which patients with low testosterone level (<250 ng/dl) were categorized as group A and the remaining patients with normal testosterone level (> 250 ng/dl) were categorized as group B. The patient demographics between the two groups are presented in the following figure.1.

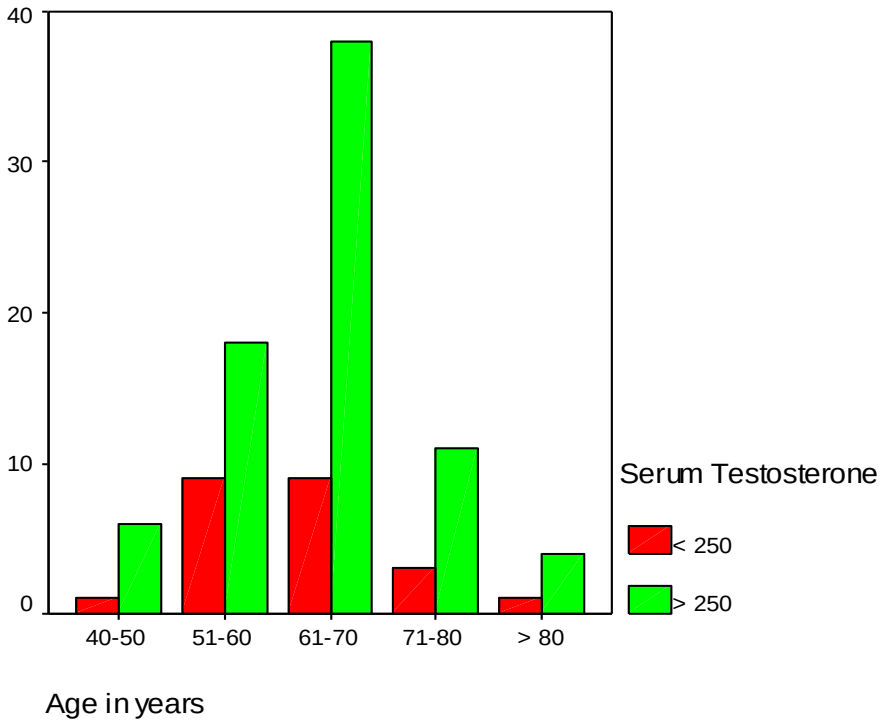

Figure.1

The patient demographics between the two groups are presented in the following table 1.

Age in years * Serum Testosterone

			Serum Testosterone		Total	P value
			< 250	> 250		
Age in years	40-50	Count	1	6	7	
		% within Age in years	14.3%	85.7%	100.0%	
		% within Serum Testosterone	4.3%	7.8%	7.0%	
	51-60	Count	9	18	27	
		% within Age in years	33.3%	66.7%	100.0%	
		% within Serum Testosterone	39.1%	23.4%	27.0%	
	61-70	Count	9	38	47	.669
		% within Age in years	19.1%	80.9%	100.0%	
		% within Serum Testosterone	39.1%	49.4%	47.0%	
	71-80	Count	3	11	14	
		% within Age in years	21.4%	78.6%	100.0%	
		% within Serum Testosterone	13.0%	14.3%	14.0%	
	> 80	Count	1	4	5	
		% within Age in years	20.0%	80.0%	100.0%	
		% within Serum Testosterone	4.3%	5.2%	5.0%	
Total		Count	23	77	100	
		% within Age in years	23.0%	77.0%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 1

The prostate cancer patients population demographics shown in above table 1.and is found not statistically significant between the two groups .The youngest age of the patient was 45 years and oldest recorded age was 85 years.

Serum PSA * Serum Testosterone

The serum PSA levels were measured in all our study patients and the PSA levels between patients with group A and group B were analyzed and the results were depicted below in table 2. The majority (74%)of patients in low testosterone group has got a serum PSA of more than 20 values compared with only 34% of patients in the corresponding group. P value is found to be statistically significant.

			Serum Testosterone		Total	P value
			< 250	> 250		
Serum PSA	< 10	Count	1	16	17	
		% within Serum PSA	5.9%	94.1%	100.0%	
		% within Serum Testosterone	4.3%	20.8%	17.0%	
	10-20	Count	5	35	40	
		% within Serum PSA	12.5%	87.5%	100.0%	
		% within Serum Testosterone	21.7%	45.5%	40.0%	**.003**
	> 20	Count	17	26	43	
		% within Serum PSA	39.5%	60.5%	100.0%	
		% within Serum Testosterone	73.9%	33.8%	43.0%	
Total		Count	23	77	100	
		% within Serum PSA	23.0%	77.0%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 2

TGS * Serum Testosterone

The comparison between patients total Gleason score (low <7,intermediate 7 and high 8-10) is shown in table.3 between two groups. Most of the patients (82.6%) in low testosterone group had a higher Gleason grade (8-10) compared to the normal testosterone group.

P value is found statistically significant (<005).

			Serum Testosterone		Total	P value
			< 250	> 250		
TGS	< 7	Count	0	34	34	
		% within TGS	.0%	100.0%	100.0%	
		% within Serum Testosterone	.0%	44.2%	34.0%	
	7	Count	4	39	43	
		% within TGS	9.3%	90.7%	100.0%	
		% within Serum Testosterone	17.4%	50.6%	43.0%	
	8-10	Count	19	4	23	<.005
		% within TGS	82.6%	17.4%	100.0%	
		% within Serum Testosterone	82.6%	5.2%	23.0%	
Total		Count	23	77	100	
		% within TGS	23.0%	77.0%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 3.

TGS * Serum Testosterone

The relation between total Gleason score (TGS) and prostate cancer patients serum testosterone levels between the two groups is shown in figure 2, as below.patients in low testosterone group had higher proportion of high gleason score compared to the normal testosterone group.

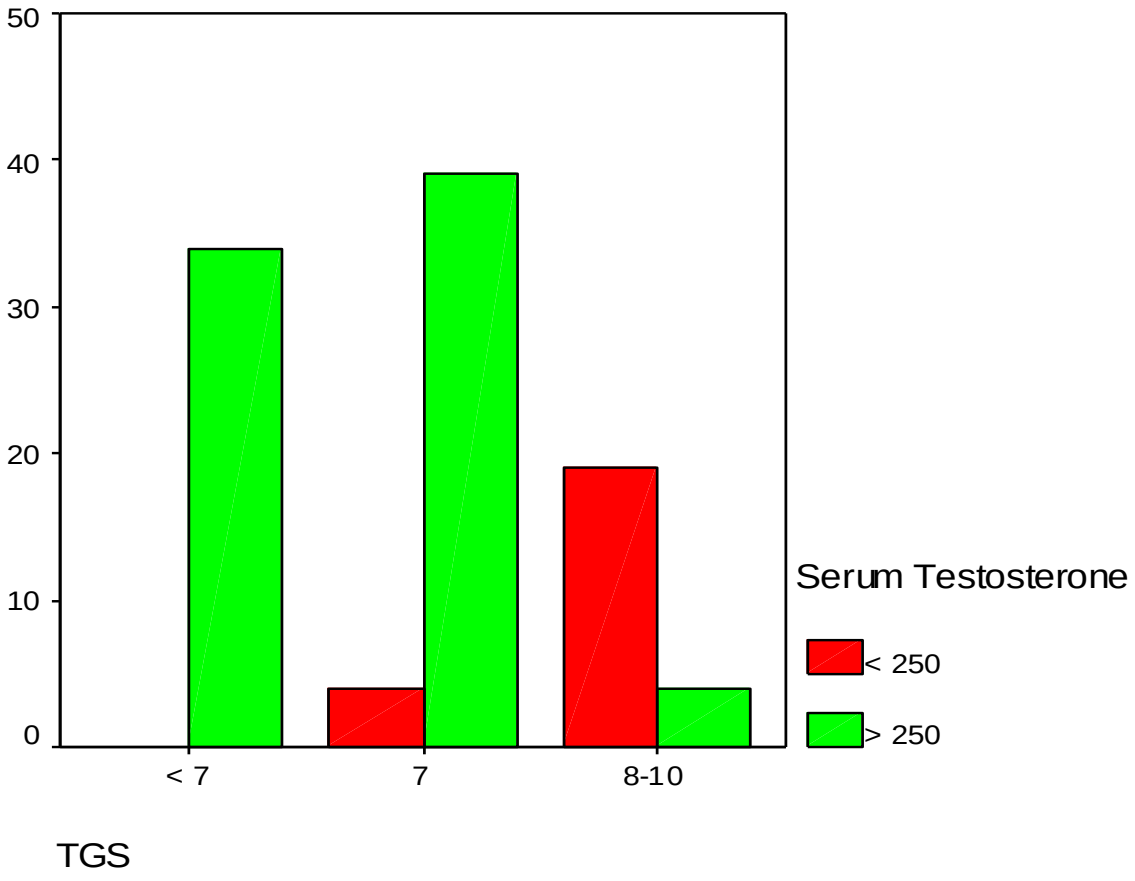

Figure 2

Clinical Stage - T * Serum Testosterone

The preoperative clinical tumour (T) status, Nodal status (N), and metastasis (M) status were analyzed and the results between the two groups were represented in table 4 as below .patients in low testosterone group had higher overall tumour stage, higher nodal stage and extensive metastases on clinical evaluation compared to the normal testosterone group. P value is found statistically significant.

			Serum Testosterone		Total	P value
			< 250	> 250		
Clinical Stage - T	T2A	Count	1	7	8	
		% within Clinical Stage - T	12.5%	87.5%	100.0%	
		% within Serum Testosterone	4.3%	9.1%	8.0%	
	T2B	Count	6	10	16	
		% within Clinical Stage - T	37.5%	62.5%	100.0%	
		% within Serum Testosterone	26.1%	13.0%	16.0%	
	T2C	Count	2	3	5	
		% within Clinical Stage - T	40.0%	60.0%	100.0%	
		% within Serum Testosterone	8.7%	3.9%	5.0%	
	T3A	Count	2	26	28	
		% within Clinical Stage - T	7.1%	92.9%	100.0%	.002
		% within Serum Testosterone	8.7%	33.8%	28.0%	
	T3B	Count	8	31	39	
		% within Clinical Stage - T	20.5%	79.5%	100.0%	
		% within Serum Testosterone	34.8%	40.3%	39.0%	
	T4A	Count	2	0	2	
		% within Clinical Stage - T	100.0%	.0%	100.0%	
		% within Serum Testosterone	8.7%	.0%	2.0%	
	T4B	Count	2	0	2	
		% within Clinical Stage - T	100.0%	.0%	100.0%	
		% within Serum Testosterone	8.7%	.0%	2.0%	
Total		Count	23	77	100	
		% within Clinical Stage - T	23.0%	77.0%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 4.

Clinical Stage - T * Serum Testosterone

Clinical tumour (T) status,Nodal status (N) were analyzed and the results between the two groups were represented in figure 3, as below.

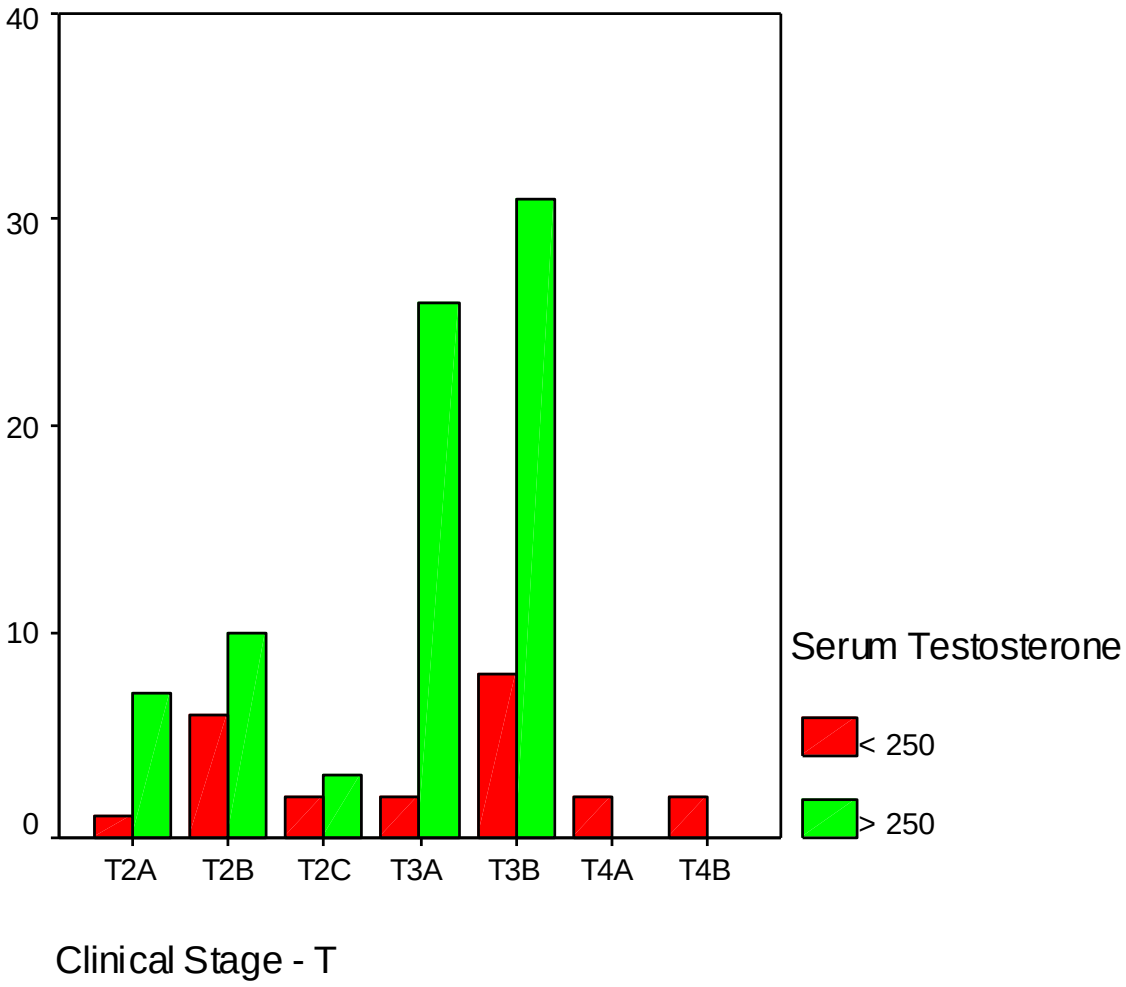

Figure 3

Clinical Stage - N * Serum Testosterone

Patients clinical Nodal status (N) were analyzed and the results between the two groups were represented in table 5,as below.group 1 patients had a higher nodal involvement than group 2 patients. P value is found statistically significant.

			Serum Testosterone		Total	P value
			< 250	> 250		
Clinical Stage - N	N0	Count	7	68	75	<0.05
		% within Clinical Stage – N	9.3%	90.7%	100.0%	
		% within Serum Testosterone	30.4%	88.3%	75.0%	
	N1	Count	16	9	25	
		% within Clinical Stage – N	64.0%	36.0%	100.0%	
		% within Serum Testosterone	69.6%	11.7%	25.0%	
Total		Count	23	77	100	
		% within Clinical Stage – N	23.0%	77.0%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 5.

Clinical Stage - N * Serum Testosterone

Patients with low serum testosterone group had more proportion of people with nodal metastasis (N 1 group) than the normal testosterone group as shown in figure 4.

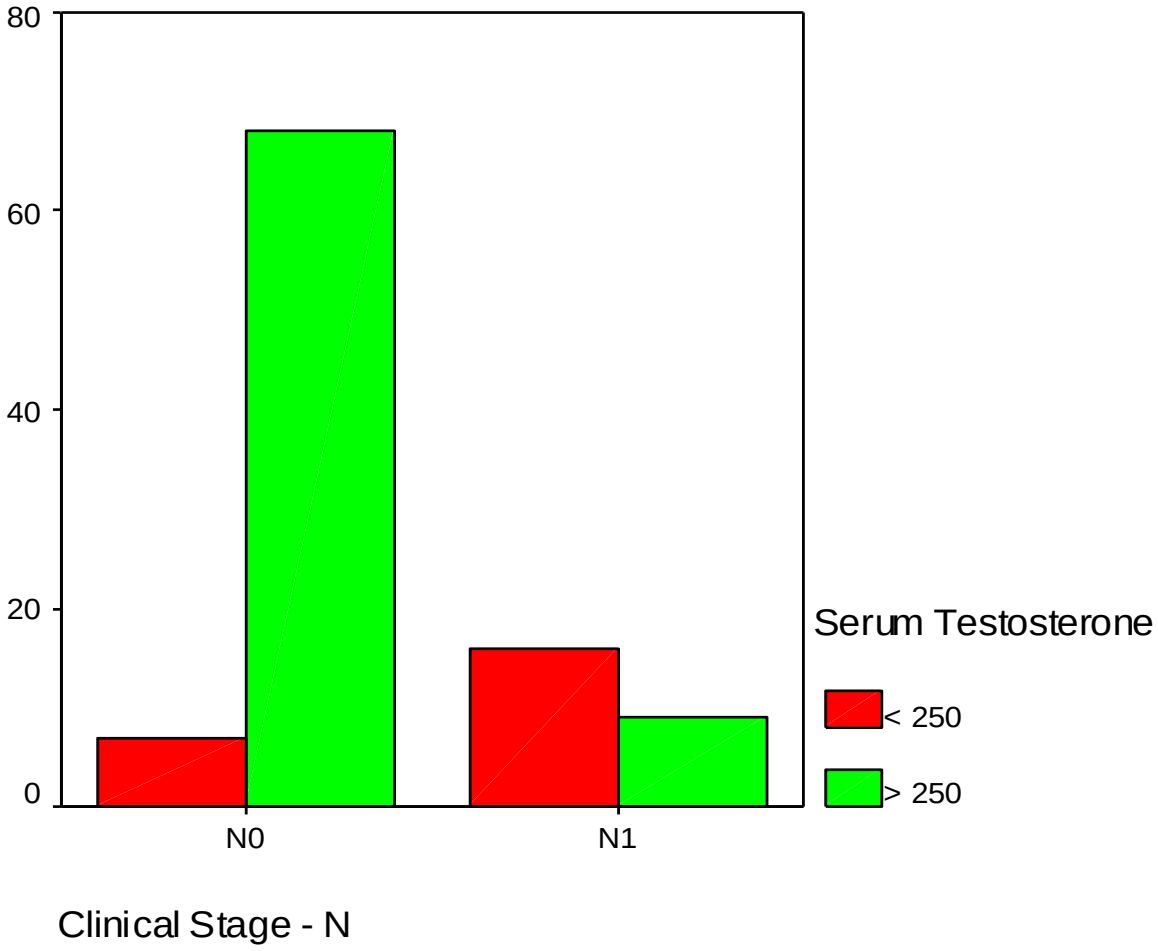

Figure 4.

Clinical Stage - M * Serum Testosterone

Patients clinical metastasis status (M) were analyzed and the results between the two groups were represented in table 6, as below. P value is found statistically significant.

			Serum Testosterone		Total	P value
			< 250	> 250		
Clinical Stage - M	M0	Count	9	64	73	
		% within Clinical Stage – M	12.3%	87.7%	100.0%	
		% within Serum Testosterone	39.1%	83.1%	73.0%	
	M1A	Count	0	1	1	
		% within Clinical Stage – M	.0%	100.0%	100.0%	
		% within Serum Testosterone	.0%	1.3%	1.0%	
	M1B	Count	11	12	23	
		% within Clinical Stage – M	47.8%	52.2%	100.0%	<.005
		% within Serum Testosterone	47.8%	15.6%	23.0%	
	M1C	Count	3	0	3	
		% within Clinical Stage – M	100.0%	.0%	100.0%	
		% within Serum Testosterone	13.0%	.0%	3.0%	
Total		Count	23	77	100	
		% within Clinical Stage – M	23.0%	77.0%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 6.

Management * Serum Testosterone

The patient management options between the low testosterone group and normal testosterone group were analyzed in the table 7 as shown below.

			Serum Testosterone		Total	P value
			< 250	> 250		
Management	RP	Count	5	6	11	.061
		% within Management	45.5%	54.5%	100.0%	
		% within Serum Testosterone	21.7%	7.8%	11.0%	
	Hormonal	Count	18	71	89	
		% within Management	20.2%	79.8%	100.0%	
		% within Serum Testosterone	78.3%	92.2%	89.0%	
Total		Count	23	77	100	
		% within Management	23.0%	77.0%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 7.

Management * Serum Testosterone

Management of patients in low serum testosterone and normal testosterone level were analyzed in following figure 5.

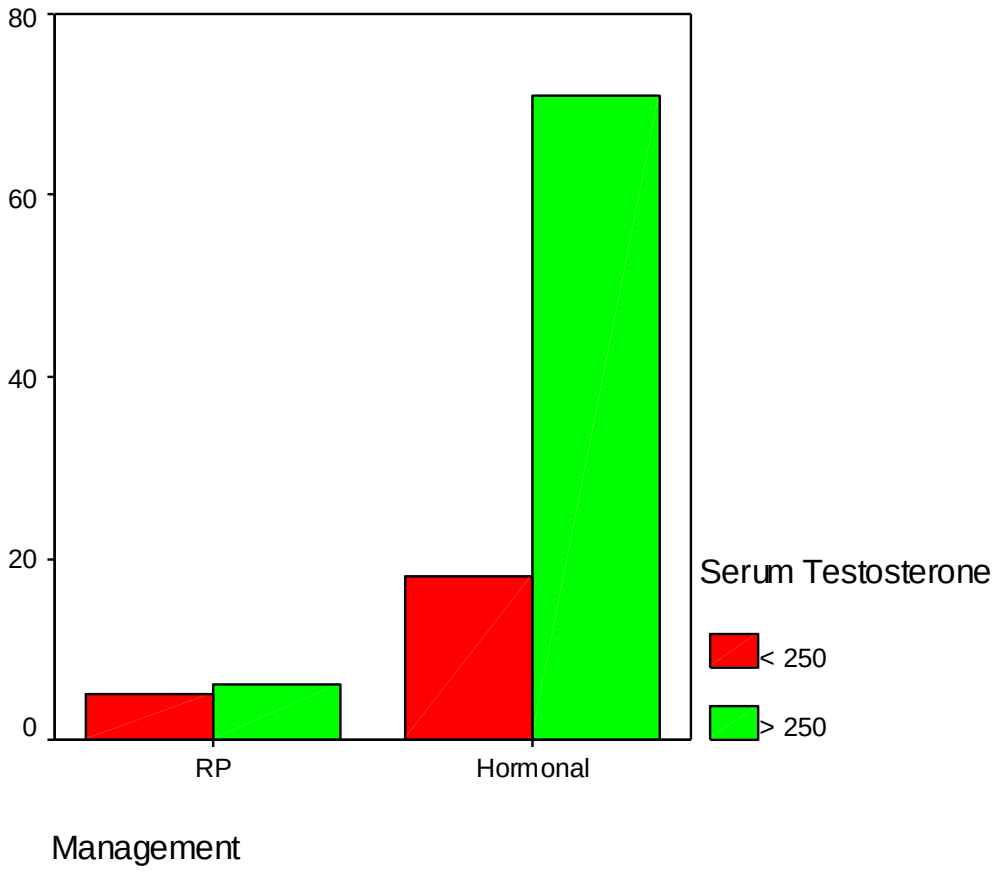

Figure 5

Pathological stage - PT * Serum Testosterone

The pathological tumour characteristics were compared between the two groups and was represented in the following table 8.Although overall pathological T staging is not statistically significant the patients in low testosterone group had higher T 3 disease than group B patients. Overall P value is not statistically Significant.

			Serum Testosterone		Total	P value
			< 250	> 250		
Pathological stage – PT	PT2A	Count	1	4	5	
		% within Pathological stage - PT	20.0%	80.0%	100.0%	
		% within Serum Testosterone	20.0%	66.7%	45.5%	
	PT3A	Count	1	1	2	
		% within Pathological stage - PT	50.0%	50.0%	100.0%	
		% within Serum Testosterone	20.0%	16.7%	18.2%	
	PT3B	Count	3	0	3	
		% within Pathological stage - PT	100.0%	.0%	100.0%	.124
		% within Serum Testosterone	60.0%	.0%	27.3%	
	PT2B	Count	0	1	1	
		% within Pathological stage - PT	.0%	100.0%	100.0%	
		% within Serum Testosterone	.0%	16.7%	9.1%	
Total		Count	5	6	11	
		% within Pathological stage - PT	45.5%	54.5%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 8.

Pathological stage - PN * Serum Testosterone

Post operative pathological nodal status between the two groups were compared as shown below in table 9. Patients in low testosterone group had more proportion of pathological lymph nodal involvement than patients in normal testosterone group. P value was found to be statistically significant (p = .015)

			Serum Testosterone		Total	P value
			< 250	> 250		
Pathological stage – PN	PN0	Count	1	6	7	.015
		% within Pathological stage - PN	14.3%	85.7%	100.0%	
		% within Serum Testosterone	20.0%	100.0%	63.6%	
	PN1	Count	4	0	4	
		% within Pathological stage - PN	100.0%	.0%	100.0%	
		% within Serum Testosterone	80.0%	.0%	36.4%	
Total		Count	5	6	11	
		% within Pathological stage – PN	45.5%	54.5%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 9.

Post operative Gleason Grade * Serum Testosterone

Post prostatectomy histopathological specimen total Gleason score between the two groups were analyzed and shown in table 10, as below. P value was found statistically significant.

			Serum Testosterone		Total	P value
			< 250	> 250		
Grade	7	Count	0	4	4	.022
		% within Grade	.0%	100.0%	100.0%	
		% within Serum Testosterone	.0%	66.7%	36.4%	
	8-10	Count	5	2	7	
		% within Grade	71.4%	28.6%	100.0%	
		% within Serum Testosterone	100.0%	33.3%	63.6%	
Total		Count	5	6	11	
		% within Grade	45.5%	54.5%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 10

Post operative Gleason Grade * Serum Testosterone

Post prostatectomy histopathological specimen total Gleason score between the two groups were analyzed and shown in the following figure 6 . P value was found statistically significant.

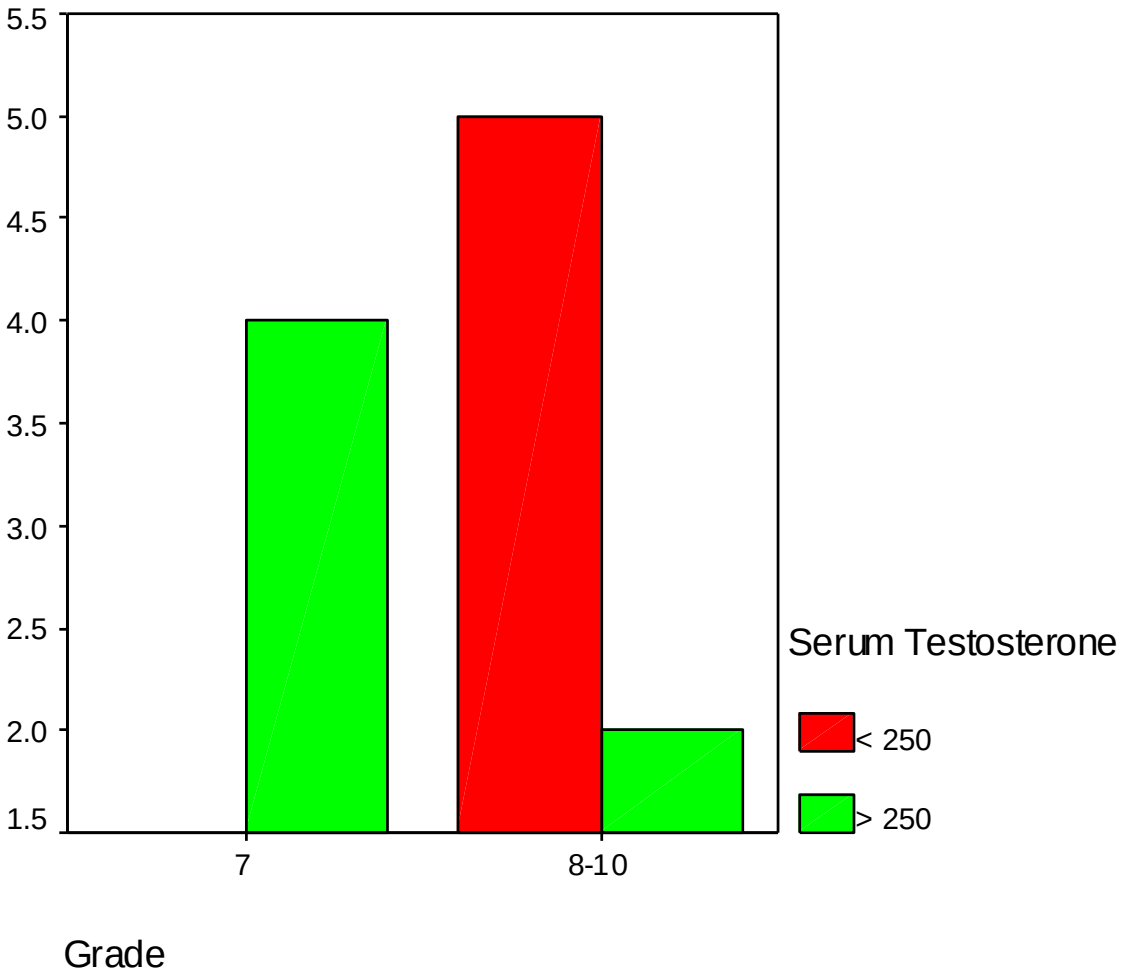

Figure 6.

SMS * Serum Testosterone

Post radical prostatectomy histopathological specimen Surgical Margin Status (SMS) between the two groups were analyzed and shown in table 11, as below. Most (> 60%) of the patients in low serum testosterone group had positive surgical margin when compared to none in normal testosterone group. P value was found statistically significant (P = .026)

			Serum Testosterone		Total	P value
			< 250	> 250		
SMS	Positive	Count	3	0	3	.026
		% within SMS	100.0%	.0%	100.0%	
		% within Serum Testosterone	60.0%	.0%	27.3%	
	Negative	Count	2	6	8	
		% within SMS	25.0%	75.0%	100.0%	
		% within Serum Testosterone	40.0%	100.0%	72.7%	
Total		Count	5	6	11	
		% within SMS	45.5%	54.5%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 11.

SMS * Serum Testosterone

The surgical margin status between the low and normal serum testosterone group were analyzed in the following figure 7.

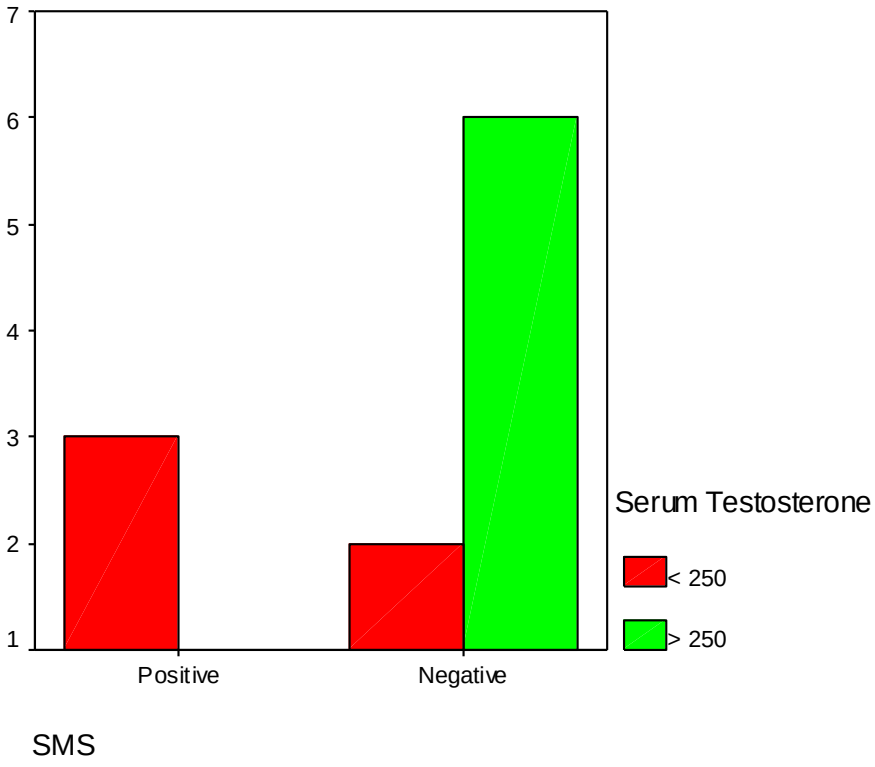

Figure 7

ECE * Serum Testosterone

Post prostatectomy histopathological specimen Extra Capsular Extension (ECE) status between the two groups were analyzed and shown in table 12,Patients with low serum testosterone group had more number of extra capsular extension than normal serum testosterone group as shown below. P value was found statistically significant.

P value = 0.036

			Serum Testosterone		Total	P value
			< 250	> 250		
ECE	Positive	Count	4	1	5	.036
		% within ECE	80.0%	20.0%	100.0%	
		% within Serum Testosterone	80.0%	16.7%	45.5%	
	Negative	Count	1	5	6	
		% within ECE	16.7%	83.3%	100.0%	
		% within Serum Testosterone	20.0%	83.3%	54.5%	
Total		Count	5	6	11	
		% within ECE	45.5%	54.5%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 12.

ECE * Serum Testosterone

Post prostatectomy histopathological specimen Extra Capsular Extension (ECE) status between the two groups were analyzed in the following figure 8 and patients in low serum testosterone group had higher positive surgical margin when compared to the normal testosterone group.

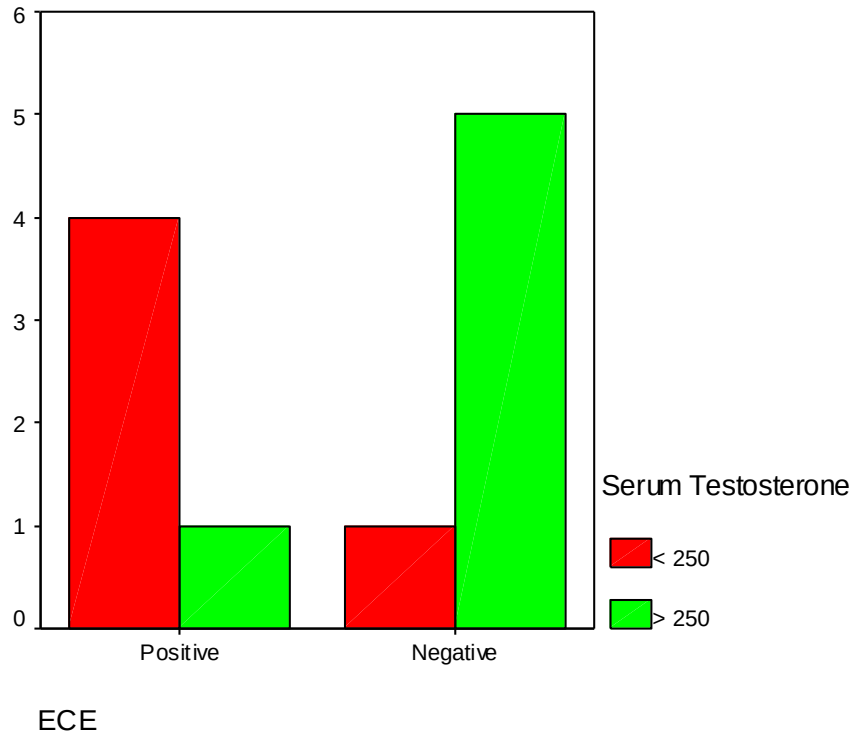

Figure 8.

SVI * Serum Testosterone

Post prostatectomy histopathological specimen Seminal Vesical Invasion (SVI) status between the two groups were analyzed and were shown in the table 13, as below.the post operative seminal Vesical invasion was more in low serum testosterone group than in normal serum testosterone group. P value was found statistically significant .

P value = .026

			Serum Testosterone		Total	P value
			< 250	> 250		
SVI	Positive	Count	3	0	3	
		% within SVI	100.0%	.0%	100.0%	
		% within Serum Testosterone	60.0%	.0%	27.3%	
	Negative	Count	2	6	8	
		% within SVI	25.0%	75.0%	100.0%	.026
		% within Serum Testosterone	40.0%	100.0%	72.7%	
Total		Count	5	6	11	
		% within SVI	45.5%	54.5%	100.0%	
		% within Serum Testosterone	100.0%	100.0%	100.0%	

Table 13.

SVI * Serum Testosterone

Post prostatectomy histopathological specimen Seminal Vesical Invasion (SVI) status between the two groups were analyzed and were depicted in figure 9, as below.the patients in group A had more seminal Vesical invasion when compared With normal serum testosterone group.

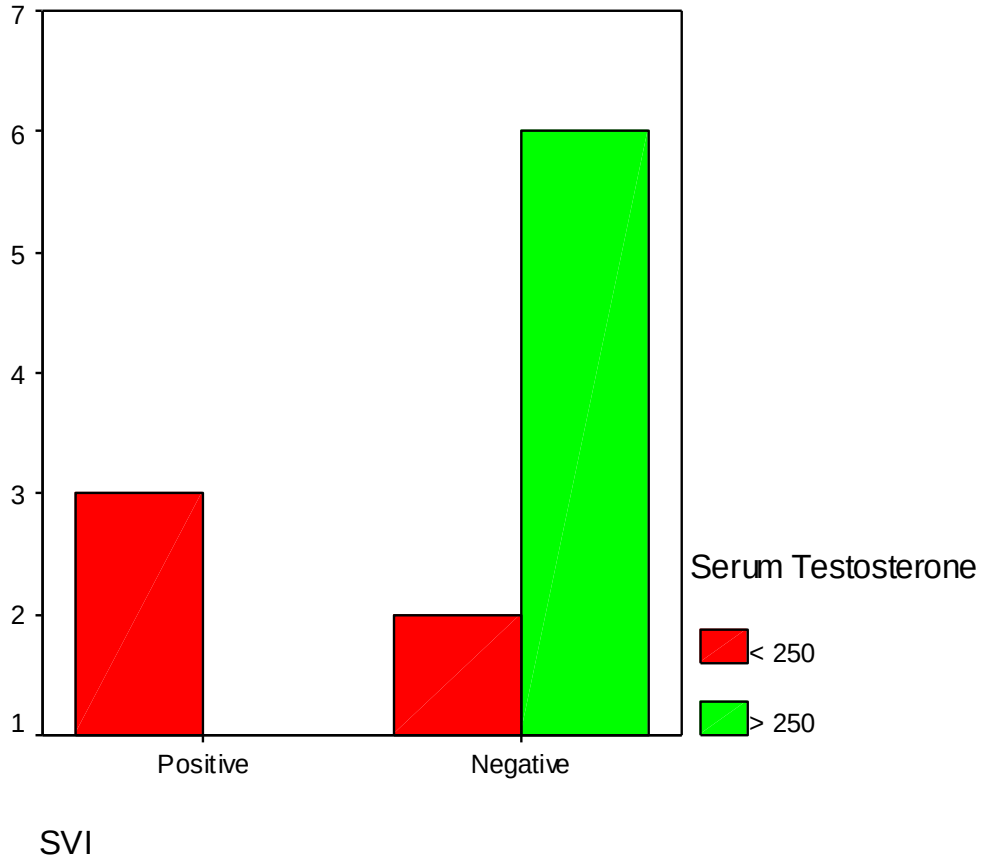

Figure 9.

DISCUSSION

The view that Serum testosterone has got a crucial part in the development of cancer prostate is controversial and widely discussed and various studies have analyzed and documented the association between low level of serum testosterone and metastatic disease and high grade cancer prostate.

Morgentaler et al. have shown a higher incidence of cancer prostate in patients with low serum testosterone. Other studies by Massachusetts aging study have reported no association between androgens including serum testosterone and cancer prostate risk.

Some of the previous studies have stated concerns about the inceased risk of prostate cancer in men with lower levels of testosterone . In patients with hypogonadal clinical status and with a PSA < 4.0 ng/ml, TRUS guided prostate biopsy has shown cancer in aruond 15%, with risk of the cancer increases twice when met with greater reduction in the serum testosterone levels.

The association between serum testosterone and cancer prostate is not yet well established. The possible explanation for the link between low serum testosterone and cancer prostate is due to the negative feedback effect of serum testosterone on hypothalamo pituitary axis. Miller et al. have shown that cancer prostate inhibits serum testosterone production by the hormone inhibin.

The association between low serum testosterone level and high-risk cancer prostate may be due to chronic disease induced hormonal change.

In our present study , patients with low serum testosterone and its association with TRUS biopsy Gleason grade, serum PSA, Clinical Tumour (T) status, Clinical nodal (N) status, Clinical metastasis(M) status ,Pathological tumour (PT) and Pathological nodal (PN) status, postoperative histo-pathological specimens Gleason total score ,Surgical margins status, extra capsular extension and Seminal vesical invasion were analyzed in comparison with normal serum testosterone patients.

The association between low level of serum testosterone and high Gleason grade prostate cancer have been demonstrated by Zhang et al.

In our study greater percentage of patients with low serum total testosterone were presented with high Gleason total scores (≥ 8).

Our study report was supported by similar to the study by Schatzl et al have shown that patients with low level of serum testosterone were found to have higher Gleason total score when plotted against normal serum testosterone.

Our study also shown that patients with low total testosterone level were associated with advanced clinical stage of the disease including clinical tumour status, nodal status and metastasis to bone and other viscera compared to patients with normal level of serum testosterone.

The results of our study were similar to previous study done by perez Marquez et al. who found that patients with low testosterone levels are at an increased risk of metastatic disease and higher risk of tumour progression.

The study by Hoffman et al. reported that patients with low serum testosterone is a marker of aggressive nature of cancer prostate.

Another study also shown that serum testosterone values are an important and independent marker in assessing prostate biopsy positivity.

The post prostatectomy histo-pathological specimens Gleason score, pathological tumour stage and baseline serum PSA are associated with an increased risk of aggressive prostate cancer.

In our study patients with low serum total testosterone were associated with higher Gleason score and less favorable pathological stage and an increased incidence of positive surgical margins in the resected specimen, extra capsular extension of tumour either unilateral or bilateral and finally positive Seminal Vesical invasion .

There are few limitations in our study which has to be taken care in future prospective studies of similar population groups. One of the limitation is small prostate cancer population size and again the number of patients who presented with low serum levels of testosterone were only 23. Second limitation of our present study is number of patients who were fit under the criteria for radical prostatectomy was only 11.Finally the follow up period up is short and it is recommended that in the future long duration studies involving larger group of patients will be helpful in confirming our current study report and also through more light on this ever debated prostate cancer study.

CONCLUSION

Low total serum testosterone is associated with higher proportion of predominant Gleason pattern 4, an indicator of aggressive prostate cancer.

Patients with low serum testosterone levels were associated with an increased serum PSA levels compared with patients in normal serum testosterone levels.

Patients with low testosterone who were managed by radical prostatectomy had a higher proportion of positive surgical margin, extra capsular extension and seminal Vesical invasion suggesting an aggressive prostate cancer behaviour.

Preoperative total testosterone should be routinely added to serum prostate specific antigen estimation to improve prostate cancer management.

BIBLIOGRAPHY

1. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin 1972;22: 232 40.
2. Huggins C, Stevens RE Jr, Hodges CV. Studies on prostatic cancer. II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg 1941;43:209–23.
3. Daniell HW. A worse prognosis for men with testicular atrophy at therapeutic orchiectomy for prostate carcinoma. Cancer 1998;83:1170–3.
4. Yamamoto S, Yonese J, Kawakami S *et al.*Preoperative serum testosterone level as an independent predictor of treatment failure following radical prostatectomy.*Eur Urol* 2007; **52**: 696–701
5. Hoffman MA, DeWolf WC, Morgentaler **A.**Is low serum free testosterone a marker for high grade prostate cancer? *J Urol*2000; **163** : 824–7
6. Schatzl G, Madersbacher S, Thurridl T *et al.* High-grade prostate cancer is associated with low serum testosterone levels.*Prostate* 2001;**47**: 52–8
7. Massengill JC, Sun L, Moul JW *et al.* Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy.*J Urol* 2003; **169**: 1670–5

8. Imamoto T, Suzuki H, Fukasawa S *et al.* Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with radical prostatectomy. *Eur Urol* 2005;**47**: 308–12

9. Isom-Batz G, Bianco FJ Jr, Kattan MW, Mulhall JP, Lilja H, Eastham JA. Testosterone as a predictor of pathological stage in clinically localized prostate cancer. *J Urol* 2005;**173** : 1935–7

10. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM. Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. *J Urol* 2005;**174** : 2178–80

11. Miller LR, Partin AW, Chan DW *et al.* Influence of radical prostatectomy on serum hormone levels. *J Urol* 1998; **160**:449–53

12. Schaeffer EM, Walsh PC. Risks of testosterone replacement. *N Engl J Med* 2004; **350**: 2004–6

13. Thompson IM, Goodman PJ, Tangen CM *et al.*The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003; **349**: 215–24

14. Rhoden EL, Morgentaler **A.** Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004; **350**: 482–92

15. Parsons JK, Carter HB, Platz EA, Wright EJ, Landis P, Metter EJ. Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 2257–60

16. Carter HB, Pearson JD, Metter EJ *et al.* Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. *Prostate* 1995; **27**:25–31

17. Marks LS, Mazer NA, Mostaghel E *et al.*Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006; **296**: 2351–61

18. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR. *et al.* Effect of testosterone supplementation on functional mobility,cognition, and other parameters in older men: a randomized controlled trial. *JAMA* 2008; **299**: 39–52

19. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* 1996; **88**: 1118–26

20. Roddam AW, Allen NE, Appleby P, Key TJ**.** Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst* 2008; **100**: 170–83

21. Yamamoto S, Yonese J, Kawakami S*et al.*Preoperative serum testosterone level as an independent predictor of treatment failure following radical prostatectomy.*Eur Urol*2007;**52**: 696–701

22. Rannikko S, Adlercreutz H. Plasma estradiol, free testosterone,sex hormone binding globulin binding capacity, and prolactin in benign prostatic hyperplasia and prostatic cancer. Prostate 1983;4:223-9.

23. Kumar VL, Wadhwa SN, Kumar V, Farooq A. Androgen, estrogen, and progesterone receptor contents and serum hormone profiles in patients with benign hypertrophy and carcinoma of the prostate. J Surg Oncol 1990;44:122-8.

24. Morgentaler A, Bruning CO 3rd, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. JAMA 1996;276:1904-6.

25. Nishiyama T, Ikarashi T, Hashimoto Y, Suzuki K, Takahashi K.Association between the dihydrotestosterone level in the prostate and prostate cancer aggressiveness using the Gleason score. J Urol 2006;176:1387-91.

26. Platz EA, Leitzmann MF, Rifai N, Kantoff PW, Chen YC, Stampfer MJ, et al. Sex steroid hormones and the androgen receptor gene CAG repeat and subsequent risk of prostate cancer in the prostate- specific antigen era. Cancer Epidemiol Biomarkers Prev 2005;14:1262-9.

27. Zhang PL, Rosen S, Veerramachaneni R, Kao J, DeWolf WC, Bubley G. Association between prostate canc Vergho DC, Heine K, Wolff JM. The role of PSA in diagnosis of prostate cancer and its recurrence.Pathologe2005;26:473-868.

28. Tricoli JV, Schoenfeldt M, Conley BA. Detection of prostate cancer and predicting progression: current and future diagnostic markers. Clin Cancer Res 2004;10:3943-53.

29. Singh AS, Chau CH, Price DK, Figg WD. Mechanisms of disease: polymorphisms of androgen regulatory genes in the development of prostate cancer. Nat Clin Pract Urol 2005;2:101-7.

30. Calais da Silva FE, Bono AV, Whelan P et al: Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Uroncological Group. Eur Urol 2009; **55:** 1269.

31. Andriole GL, Bostwick DG, Brawley OW et al: Effect of dutasteride on the risk of prostate cancer. REDUCE Study Group. N Engl J Med 2010; **362:** 1192.

32. Lackner JE, Maerk I, Koller A et al: Serum inhibin—not a cause of low testosterone levels in hypogonadal prostate cancer? Urology 2008; **72:** 1121.

33. Rosner W, Auchus RJ, Azziz R et al: Position statement: utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. J Clin Endocrinol Metab 2007; **92:** 405.

34. Araujo AB, Esche GR, Kupelian V et al: Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab 2007; **92:** 4241.

35. Wang C, Nieschlag E, Swerdloff R et al: Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol 2008; **159:** 507.

36. Wright JL, Salinas CA, Lin DW et al: Prostate cancer specific mortality and Gleason 7 disease differences in prostate cancer outcomes between cases with Gleason 4 _ 3 and Gleason 3 _ 4 tumors in a population based cohort. J Urol 2009; **182:** 2702.

37. Partin AW, Kattan MW, Subong EN et al: Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update.JAMA 1997; **277:** 1445.

38. Rasiah KK, Stricker PD, Haynes AM et al: Prognostic significance of Gleason pattern in patients with Gleason score 7 prostate carcinoma. Cancer 2003; **98:** 2560.

39. Iversen P, Rasmussen F and Christensen IJ: Serum testosterone as a prognostic factor in patients with advanced prostatic carcinoma. Scand J Urol Nephrol Suppl 1994; **157:** 41.

40. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predictfor a poor outcome in metastatic prostate cancer. Am J Clin Oncol 1997;20:605-608.

41. Zhang PL, Rosen S, Veeramachaneni R, et al. Association between prostate cancer and serum testosterone levels. Prostate 2002;53:179-182.

42. Perez Marquez M, Garcia-Cruz E, Piqueras Bartolome M, et al. Low testosterone levels are associated with poor prognosis risk factors on needle prostate cancer biopsies. J Men's Health 2009;3:252.

43. Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. Prostate 1995;27(1):25-27

44. Schatzl G, Madersbacher S, Haitel A, et al. Associations of serum testosterone with micro vessel density, androgen receptor density and androgen receptor gene polymorphism in prostate cancer. J Urol 2003;169:1312-1315.

45. Marberger M, Roehrborn CG, Marks LS, et al. Relationship among serum testosterone, sexual function, and response to treatment in men receiving dutasteride for benign prostatic hyperplasia. J Clin Endocrinol Metab 2006;91:1323–8.

46. Hovenanian MS, Deming CL. The heterologous growth of cancer of the human prostate. Surg Gynecol Obstet 1948;86:29–35.

47. Sharkey DA, Fisher ER. Carcinoma of the prostate in the absence of testicular tissue. J Urol 1960;83:468–70.

INFORMED CONSENT FORM

Title of the study:

"A study of association of low serum testosterone and prostate cancer behaviour"

Name of the Participant:

Name of the Principal Investigator : Dr.K.ARUNPRASAD

Name of the Institution : Rajiv Gandhi Govt. General Hospital, Chennai -3.

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in **"A study of association of low serum testosterone and prostate cancer behaviour"**

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 3 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.
8. I have not participated in any research study within the past 6 month(s)
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.

12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
13. I have understand that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____

Date_____

Name and Signature of impartial witness (required for illiterate patients):
Name _____ Signature_____
Date_____

Address and contact number of the impartial witness:
Name and Signature of the investigator or his representative obtaining consent:
Name _____ Signature_____
Date_____

Address and contact number of the impartial witness:
_____
Name and Signature of the investigator or his representative obtaining consent:
Name _____ Signature_____
Date_____

<u>ஆராய்ச்சி ஒப்புதல் கடிதம்</u>

சுக்கிய (ப்ராஸ்டேட்) சுரப்பி புற்றுநோயிற்கும் குறைந்த அளவு டெஸ்டோஸ்டிரோன் சுரப்பி நீருக்கும் உள்ள தொடர்பை கண்டறியும் ஆராய்ச்சி

பெயர்	:	தேதி	:
வயது	:	உள் / புற நோயாளி எண்	:
பால்	:	ஆராய்ச்சி சேர்க்கை எண்	:

இந்த ஆராய்ச்சின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

சுக்கிய (ப்ராஸ்டேட்) சுரப்பி புற்றுநோயிற்கும் குறைந்த அளவு டெஸ்டோஸ்டிரோன் சுரப்பி நீருக்கும் உள்ள தொடர்பை கண்டறியும் ஆராய்ச்சிக்கு தேவையான அனைத்து விவரங்களையும் தெரியப்படுத்துவதற்கு நான் முழுசம்மதம் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

சுக்கிய (ப்ராஸ்டேட்) சுரப்பி புற்றுநோயிற்கும் குறைந்த அளவு டெஸ்டோஸ்டிரோன் சுரப்பி நீருக்கும் உள்ள தொடர்பை கண்டறியும் ஆராய்ச்சி பற்றிய தகவல் தாளை நான் பெற்றுக் கொண்டேன்.

இந்த ஆராய்ச்சியினால் ஏற்படும் நன்மைகளையும், சில பக்கவிளைவுகளையும் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்து கொண்டேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம்.

.....	.....	.....
நோயாளியின் பெயர்	கையொப்பம்/ இடது பெருவிரல் ரேகை	தேதி

.....	.....	.....
ஆராய்ச்சியாளரின் பெயர்	கையொப்பம்	தேதி

<u>ஆராய்ச்சி தகவல் தாள்</u>

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவனையில், சுக்கிய (ப்ராஸ்டேட்) சுரப்பி புற்றுநோயிற்கும் குறைந்த அளவு டெஸ்டோஸ்டிரோன் சுரப்பி நீருக்கும் உள்ள தொடர்பை கண்டறியும் ஆராய்ச்சி இங்கு நடைபெற்று வருகின்றது.

நீங்களும் ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் தங்களின் கேள்விகள் கேட்கபட்டு அதன் தகவல்களையும் முடிவுகளையும் ஆராய்வோம். அதனால் தங்கள் சிகிச்சைக்கு எவ்வித பாதிப்பும் ஏற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியின்போது தங்களிடமிருந்து உடல்நலபரிசோதனைக்கு தேவையான இரத்தம் எடுக்கும்போது இந்த டெஸ்டோஸ்டிரோன் சுரப்பி நீர் கண்டறிய தேவையான இரத்தம் எடுக்கபடும் என்பதையும், அதனால் எவ்வித பாதிப்பும் ஏற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு பலன்களை/ முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

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ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

INFORMATION TO PARTICIPANTS

SPONSOR : NIL

Investigator: Dr.K. ARUNPRASAD

Name of Participant:

Title: "A study of association of low serum testosterone and prostate cancer behaviour"

You are invited to take part in this study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns. You are being asked to participate in this study being conducted in Madras Medical College and Rajiv Gandhi Government General Hospital Chennai-3.

What is the Purpose of the Research?

1. To evaluate the relationship between low levels of hormone testosterone in blood and prostate cancer behaviour and

2. To study the correlation between low levels of hormone testosterone in blood and tumour marker PSA. We have obtained permission from the Institutional Ethics Committee.

The Study Design

Patients: All Transrectal Ultrasound guided biopsy proven cases of prostate cancer with low serum testosterone level with age more than 40 years

Control: All Transrectal Ultrasound guided biopsy proven cases of prostate cancer with normal serum testosterone level with age more than 40 years

Study Procedures

Inclusion Criteria:

All newly diagnosed prostate cancer patients (Trans rectal ultrasound guided biopsy proved) in our institution will be enrolled

Exclusion Criteria:

- Patients already on testosterone replacement therapy
- Patients on other hormonal therapy
- Patients taking medications known to lower PSA (finasteride or dutasteride) were excluded from this study.

Possible Risks to you - Briefly Mention: Nil

Possible benefits to you:

The results of the study may help you in better planning of hormonal ablative treatment options and better patient outcome

Possible benefits to other people

The result of the research may provide benefits to the society in terms of advancement of medical knowledge and / or therapeutic benefits to future patient for better management of prostate cancer

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, IEC and any person or agency required by law like the Drug Controller General of India to view your data, if required. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decisions to not participate in this research study will not affect your medical care or your relationship with investigator or the institution. Your doctor will still take care of you and you will not loose any benefits to which you are entitled.

PROFORMA

"A STUDY OF ASSOCIATION OF LOW SERUM TESTOSTERONE AND PROSTATE CANCER BEHAVIOUR"

- SL No. : Date :
- Patient name : Age/sex :
- IP .NO :
- Address :
- Chief complaints :
- Presenting illness :
- Past medical /surgical history :
- Previous H/O TRUS Biopsy :
- Personal history :
- Family history :
- General examination :
- Pulse : BP:
- P/A : E/G:
- DRE:

INVESTIGATIONS

- HB
- TC
- DC
- ESR

Urine R/E :

Urine C&S :

- RBS
- Blood urea
- Serum creatinine
- Serum Electrolytes
- USG KUB/TRUS
- TRUS biopsy report (Gleason score)
- Serum Testosterone
- Serum PSA
- Other findings
- X-rays
- Bone scan
- CECT/MRI abdomen

The 2009 TNM (Tumour Node Metastasis) classification for PCa is shown in Table 3 (1).

Table 3: Tumour Node Metastasis (TNM) classification of PCa*

T - Primary tumour		
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1		Clinically inapparent tumour not palpable or visible by imaging
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA] level)
T2		Tumour confined within the prostate[1]
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3		Tumour extends through the prostatic capsule[2]
	T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
	T3b	Tumour invades seminal vesicle(s)
T4		Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional lymph nodes[3]		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
M - Distant metastasis[4]		
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

1 *Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.*

2 *Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.*

Sl no.	Name	Age/Sex	IP no	Serum PSA		SG	TGS	Serum Testostrone	Clinical Stage			MANAGEMENT	Pathological Stage						
					PG				T	N	M		PT	PN	M	TGS	SMS	ECE	SVI
1	DHAKSHINAMOORTHY	60/M	56829	24.06	4	4	8	193.6	T3A	N1	M1B	HORMONAL							
2	ARJUNAN	55/M	56013	21.7	3	3	6	656.4	T2A	N0	M1B	HORMONAL							
3	BOOPALAN	55/M	62037	18.2	4	4	8	173.2	T3B	N0	M0	HORMONAL							
4	JANARTHANAN	68/M	67907	31.8	3	3	6	443.1	T2A	N0	M1A	HORMONAL							
5	SANDHYAGU	58/M	56621	25.9	3	4	7	674.6	T3B	N0	M0	HORMONAL							
6	ARJUN	55/M	51080	28.6	3	3	6	492.3	T3A	N1	M0	HORMONAL							
7	RAJAMANI	45/M	35806	11.8	3	3	6	640.8	T3B	N0	M0	HORMONAL							
8	GOVINDHAN	78/M	27747	26.7	3	4	7	723.4	T2B	N0	M1B	HORMONAL							
9	ETHIRAJ	68/M	31168	14.6	4	4	8	187.4	T2B	N0	M0	RP	**PT3B**	**PN1**	**M0**	8	N	P	P
10	IBRAHIM SHERIFF	70/M	51168	16.2	3	3	6	447.8	T3A	N1	M0	HORMONAL							
11	KUMAR	52/M	58723	12.6	3	3	6	654.3	T3B	N0	M0	HORMONAL							
12	KRISHNAN	75/M	22513	7.1	3	3	6	411.3	T3B	N0	M0	HORMONAL							
13	PADMANABAN	85/M	39505	26.4	3	4	7	387.1	T2C	N1	M0	HORMONAL							
14	KRISHNAN	60/M	89016	82.4	4	5	9	146.4	T3B	N1	M1C	HORMONAL							
15	ARUNAGIRI	68/M	67221	21.7	3	3	6	512.3	T2A	N0	M1B	HORMONAL							
16	KUPPUSAMY	65/M	14043	15.3	3	3	6	437.1	T3A	N0	M0	HORMONAL							
17	GOPAL	60/M	14043	18.4	3	3	6	816.1	T3B	N0	M0	HORMONAL							
18	PAULRAJ	65/M	65918	31.9	4	4	8	157.6	T3B	N1	M1B	HORMONAL							
19	PERUMAL	60/M	50979	11.2	4	5	9	142.7	T2A	N0	M0	RP	**PT3B**	**PN1**	**M0**	10	P	P	P
20	KRISHNAN	61/M	28148	25.4	3	3	6	776.1	T3A	N0	M1B	HORMONAL							
21	VAIYABURI	76/M	95813	19.4	3	4	7	694.6	T3B	N0	M0	HORMONAL							
22	KRISHNAMOORTHY	64/M	90427	28.4	3	4	7	590.6	T2B	N0	M1B	HORMONAL							
23	VEERASAMY	70/M	12179	9.1	3	4	7	394.5	T2B	N0	M0	RP	**PT2B**	**PN0**	**M0**	7	N	N	N
24	JEYAKUMAR	74/M	25367	8.6	3	3	6	647.4	T3A	N0	M0	HORMONAL							
25	PULLAIAH	70/M	19081	43.8	4	4	8	173.6	T3B	N1	M1B	HORMONAL							
26	ANBAZHAGAN	59/M	15432	21.2	3	4	7	594.3	T2A	N0	M1B	HORMONAL							
27	KRISHNAKUMAR	75/M	14309	24.3	3	4	7	137.4	T3A	N1	M1B	HORMONAL							
28	JEYACHANDRAN	65/M	12006	29.8	3	3	6	347.7	T2B	N0	M1B	HORMONAL							
29	DURAI	58/M	11032	31.2	4	4	8	164.3	T2B	N0	M1B	HORMONAL							
30	ABDULATEEF	62/M	12015	33.1	3	3	6	540.1	T2A	N0	M1B	HORMONAL							
31	KRISHNAMOORTHY	74/M	61479	28.6	4	4	8	153.4	T2B	N1	M0	HORMONAL							
32	MUNUSAMY	68/M	24498	13.6	4	3	7	497.6	T3A	N0	M0	HORMONAL							
33	DHAKSHINAMOORTHY	70/M	56826	11.6	3	3	6	461.2	T3B	N0	M0	RP	**PT2B**	**PN0**	**M0**	7	N	N	N
34	APPARAO	75/M	11864	51.4	5	5	10	86.8	T4A	N1	M1C	HORMONAL							
35	RAJAN	63/M	81610	16.8	3	3	6	467.4	T3A	N1	M0	HORMONAL							
36	KOTHANDARAMAN	85/M	13086	25.4	3	4	7	541.6	T3B	N0	M0	HORMONAL							
37	SUNDARRAJ	57/M	11847	14.3	4	3	7	379.1	T3B	N0	M0	HORMONAL							
38	DURAI	56/M	16025	14.6	3	4	7	297.2	T3A	N0	M0	HORMONAL							
39	PATTU	51/M	10881	28.7	5	4	9	100.4	T3B	N1	M1B	HORMONAL							
40	ELUMALAI	55/M	53201	26.3	4	4	8	391.3	T3A	N0	M0	HORMONAL							
41	VENUGOPAL	46/M	58902	5.2	4	4	8	119.4	T2B	N0	M0	RP	**PT3B**	**PN1**	**M0**	9	P	P	P
42	VARADHAN	48/M	98964	19.4	3	4	7	641.1	T3B	N0	M0	HORMONAL							
43	SAMINATHAN	58/M	95006	16.1	3	3	6	520.3	T3B	N0	M0	HORMONAL							

Sl no.	Name	Age/Sex	IP no	Serum PSA		SG	TGS	Serum Testostrone	Clinical Stage			MANAGEMENT	Pathological Stage						
					PG				T	N	M		PT	PN	M	TGS	SMS	ECE	SVI
44	RAMAMOORHTY	56/M	10634	7.8	3	4	7	418.2	T3B	N0	M0	HORMONAL							
45	SUBRAMANI	58/M	18990	24.3	4	4	8	396.9	T3A	N0	M1B	HORMONAL							
46	SELVAM	60/M	98813	36.7	4	4	8	117.2	T4A	N1	M1B	HORMONAL							
47	JEYARAMAN	74/M	94990	13.2	3	4	7	294.3	T3A	N0	M0	HORMONAL							
48	GOVINDASAMY	70/M	96230	15.4	4	3	7	397.1	T3A	N0	M0	HORMONAL							
49	ISMAIL	66/M	34266	11.6	3	3	6	647.3	T2B	N0	M0	RP	**PT2B**	**PN0**	**M0**	7	N	N	N
50	SENGAPPAN	65/M	30054	13.6	4	3	7	384.6	T3B	N0	M0	HORMONAL							
51	SUNDARAM	68/M	10410	17.9	3	3	6	446.4	T3A	N0	M0	HORMONAL							
52	RAMAKRISHNAN	70/M	18910	28.2	3	4	7	720.4	T2B	N1	M1B	HORMONAL							
53	CHANDRAMOHAN	65/M	10517	36.4	4	3	7	477.4	T2B	N0	M1B	HORMONAL							
54	CHINNASAMY	62/M	11296	13.1	3	4	7	399.1	T3B	N0	M0	HORMONAL							
55	PADAMANABAN	64/M	62596	43.4	4	5	9	148.4	T3B	N1	M1B	HORMONAL							
56	KALIYAPPAN	57/M	96721	9.4	4	3	7	794.3	T3A	N0	M0	HORMONAL							
57	JEYACHANDRAN	62/M	89426	34.2	4	4	8	543.4	T3B	N1	M0	HORMONAL							
58	RAJANGAM	62/m	61223	56.2	5	4	9	139.4	T4B	N1	M1C	HORMONAL							
59	LOGANATHAN	50/M	10789	18.6	3	4	7	364.8	T3A	N0	M0	HORMONAL							
60	SIVARAMAN	62/M	11083	11.4	3	3	6	561.6	T3B	N0	M0	HORMONAL							
61	PERUMAL	68/M	10523	8.6	3	3	6	399.6	T3A	N0	M0	HORMONAL							
62	PONNUSAMY	55/M	11957	14.7	4	3	7	129.6	T2B	N0	M0	RP	**PT2B**	**PN0**	**M0**	8	N	N	N
63	SUBRAMANI	64/M	20542	14.3	3	4	7	467.6	T3B	N0	M0	HORMONAL							
64	GOVINDHAN	61/M	50812	26.5	4	4	8	100.4	T3B	N1	M0	HORMONAL							
65	ALLIAPPAN	75/M	16905	26.4	3	4	7	764.3	T3B	N0	M0	HORMONAL							
66	HAMEED	65/M	15063	13.6	4	4	8	593.6	T3A	N0	M0	HORMONAL							
67	PAMMAL	65/M	69110	6.8	3	3	6	654.6	T2B	N0	M0	HORMONAL							
68	RAJI GOUNDER	50/M	50662	13.9	3	3	6	344.6	T3A	N0	M0	HORMONAL							
69	CHENGALRAJ	48/M	41438	11.6	3	4	7	651.6	T3B	N0	M0	HORMONAL							
70	KUMAIYAN	68/M	43508	7.4	3	3	6	721.3	T3B	N0	M0	HORMONAL							
71	RATHINAM	65/M	27764	23.4	3	3	6	495.3	T3A	N1	M0	HORMONAL							
72	RAGHAVAN	69/M	74810	12.6	3	4	7	394.4	T2A	N0	M0	RP	**PT2B**	**PN0**	**M0**	7	N	N	N
73	DIWAKARAN	74/M	29081	12.4	4	3	7	711.4	T2B	N0	M0	HORMONAL							
74	ROSE NAIDU	82/M	10639	96.4	4	4	8	48.3	T4B	N1	M1B	HORMONAL							
75	VENKATACHALAM	64/M	11063	8.4	3	3	6	621.4	T3B	N0	M0	HORMONAL							
76	PALANIYAPPAN	70/M	18612	16.2	3	4	7	576.4	T3B	N0	M0	HORMONAL							
77	KUMAR	59/M	72610	16.3	4	3	7	384.6	T3A	N1	M0	HORMONAL							
78	PURUSHOTHAMAN	64/M	50782	8.4	3	3	6	396.4	T3A	N0	M0	HORMONAL							
79	ANANDHAN	66/M	41487	37.1	4	3	7	212.6	T2C	N1	M1B	HORMONAL							
80	NATARAJAN	72/M	23112	24.8	4	3	7	716.4	T3B	N0	M0	HORMONAL							
81	GANESAN	75/M	34278	6.5	3	3	6	427.4	T3A	N0	M0	HORMONAL							
82	KRISHNAN	65/M	22178	14.7	4	3	7	154.6	T2B	N0	M0	RP	**PT3A**	**PN1**	**M0**	9	P	P	N
83	BALASUNDARAM	85/M	10759	17.6	3	3	6	347.4	T3A	N0	M0	HORMONAL							
84	SUBBARAYAN	70/M	91404	13.4	4	3	7	459.4	T3B	N0	M0	HORMONAL							
85	MURUGAVEL	65/M	27891	18.6	3	4	7	724.4	T3A	N0	M0	HORMONAL							
86	PALANI KUMAR	71/M	74213	9.3	3	3	6	436.4	T3B	N0	M0	HORMONAL							

Sl no.	Name	Age/Sex	IP no	Serum PSA		SG	TGS	Serum Testostrone	Clinical Stage			MANAGEMENT	Pathological Stage						
					PG				T	N	M		PT	PN	M	TGS	SMS	ECE	SVI
87	ABDUL MAJITH	56/M	83049	24.3	4	4	8	174.6	T2C	N1	M1B	HORMONAL							
88	RAMAKRISHNAN	62/M	56190	21.6	3	3	6	556.4	T3A	N0	M0	HORMONAL							
89	PREM PRASAD	51/M	47838	26.4	4	3	7	636.4	T3B	N0	M0	HORMONAL							
90	SUNDARAM	46/M	50610	21.2	3	3	6	394.6	T2C	N1	M0	HORMONAL							
91	MUTHUPANDI	59/M	56998	13.6	3	4	7	439.6	T2B	N0	M0	RP	**PT3A**	**PN0**	**M0**	8	N	P	N
92	VELAYUDHAM	75/M	50670	12.4	3	4	7	712.4	T3B	N0	M0	HORMONAL							
93	SUBBAIAH	82/M	60835	21.4	4	3	7	556.4	T2C	N0	M0	HORMONAL							
94	SUBRAMANI	60/M	83176	7.6	4	3	7	396.8	T2A	N0	M0	RP	**PT2B**	**PN0**	**M0**	8	N	N	N
95	ESWARAN	65/M	59436	9.4	3	4	7	394.3	T3B	N0	M0	HORMONAL							
96	VENKATESAN	69/M	28756	19.2	4	3	7	431.6	T3B	N0	M0	HORMONAL							
97	MUNUSAMY	70/M	84782	26.2	4	4	8	168.6	T3B	N1	M0	HORMONAL							
98	DURAI KANNAN	70/M	89614	8.2	3	3	6	374.4	T3B	N0	M0	HORMONAL							
99	VELLAI	65/M	84381	21.4	3	4	7	398.6	T3A	N0	M1B	HORMONAL							
100	RAMAN	60/M	96242	7.6	3	3	6	347.3	T3B	N0	M0	HORMONAL							

ABBREVIATIONS

T-TUMOUR
N-NODAL STATUS
M-METASTASIS
PG-PRIMARY GLEASON SCORE
SG-SECONDARY GLESON SCORE
TGS-TOTAL GLEASON SCORE

PT-PTHOLOGICAL TUMOUR
PN-PATHOLOGICAL NODE

SMS-SURGICAL MARGIN STATUS
ECE-EXTRA CAPSULAR EXTENSION
SVI-SEMINAL VESICAL INVATION

RP-RADICAL PROSTATECTOMY
P-POSITIVE
N-NEGATIVE

LIST OF ABBRIEVIATIONS

PSA- Prostate specific antigen

DRE- Digital rectal examination

TRUS- Transrectal ultrasonography

TGS- Total Gleason score

CT- Clinical tumour status

CN-Clinical nodal status

M- Metastasis

PT- pathological tumour status

PN- Pathological nodal status

ECE- Extra capsular extension

SMS- Surgical margin status

SVI- Seminal Vesical invasion

BPH - Benign prostatic hyperplasia

LUTS - lower urinary tract symptoms

A STUDY OF ASSOCIATION OF LOW SERUM TESTOSTERONE AND PROSTATE CANCER BEHAVIOUR

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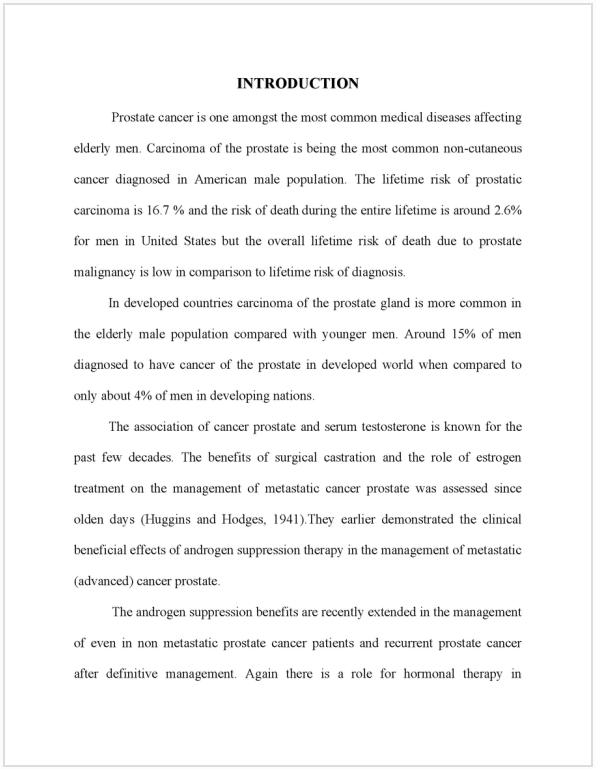

INTRODUCTION

Prostate cancer is one amongst the most common medical diseases affecting elderly men. Carcinoma of the prostate is being the most common non-cutaneous cancer diagnosed in American male population. The lifetime risk of prostatic carcinoma is 16.7 % and the risk of death during the entire lifetime is around 2.6% for men in United States but the overall lifetime risk of death due to prostate malignancy is low in comparison to lifetime risk of diagnosis.

In developed countries carcinoma of the prostate gland is more common in the elderly male population compared with younger men. Around 15% of men diagnosed to have cancer of the prostate in developed world when compared to only about 4% of men in developing nations.

The association of cancer prostate and serum testosterone is known for the past few decades. The benefits of surgical castration and the role of estrogen treatment on the management of metastatic cancer prostate was assessed since olden days (Huggins and Hodges, 1941).They earlier demonstrated the clinical beneficial effects of androgen suppression therapy in the management of metastatic (advanced) cancer prostate.

The androgen suppression benefits are recently extended in the management of even in non metastatic prostate cancer patients and recurrent prostate cancer after definitive management. Again there is a role for hormonal therapy in